Settima edizione di

G.d.L. Biologia Cellulare Molecolare

AIEOP

ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP...

...in Lab

Nuovi trattamenti basati sulla medicina di precisione nei bambini affetti da tumore

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S.C. Pediatria Oncologica
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano

Milano, 22 e 23 maggio 2026

Nessun conflitto di interesse da dichiarare

La ricerca clinica in oncologia pediatrica

- Difficoltà nella conduzione di studi clinici con farmaci innovativi
- Limitato interesse delle case farmaceutiche
  - *mercato ristretto*
  - *scarsi profitti*
  - *reclutamento lento*
- Scarso supporto degli enti regolatori

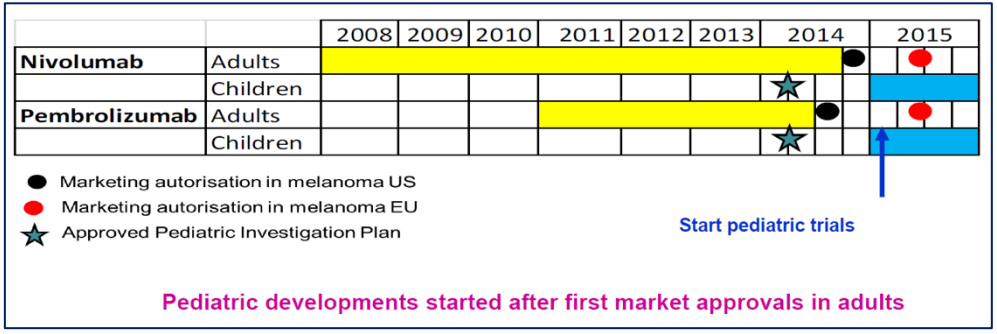
- Poche nuove molecole studiate nell'adulto sono offerte per studi pediatrici e con un "gap" temporale notevole
- Pochi trials clinici di fase precoce (I-II) sono condotti e con il coinvolgimento di un numero limitato di pazienti

La ricerca clinica in oncologia pediatrica

"GAP" NUMERICO

Pediatric phase I studies *(Lee et al., J Clin Oncol, 23, 8431, 2005)*	Adult phase I studies *(Horstmann E. et al., NEJM, 352, 892-904, 2005)*
Period: 1990-2004 **69 studies, 1.973 patients**	Period: 1991-2002 **460 studies, 11.935 patients**
55 single agent, 14 combinations	193 single agent, 267 combinations

"GAP" TEMPORALE



La ricerca clinica in oncologia pediatrica

Table 1. Targeted therapies approved by the FDA and/or EMA for pediatric cancer

Drug	Pediatric indication	Year approved		Pediatric phase I[a] response rate in targeted population	Number of patients
		FDA	EMA		
Tretinoin	Acute promyelocytic leukemia (APML)	1995	NC	83% (all CR; ref. 101)	6
Everolimus	Subependymal giant cell astrocytoma (SEGA)	2010	2011	75% (102)	28
Dinutuximab	Neuroblastoma	2015	2015[b]	66% (103)	6
Blinatumomab	Relapsed/refractory (R/R) B acute lympho-blastic leukemia (ALL)	2016	2015	30% (all minimal residual disease negative; ref. 21)	23
Pembrolizumab	R/R classic Hodgkin Lymphoma, primary mediastinal B-cell lymphoma, Merkel cell carcinoma, MSI-high tumors	2017	N/A	60% (Hodgkin; ref. 66)	15
Ipilimumab	Melanoma (≥12 years)	2017	2017	0 (67)	12
Gemtuzumab	R/R acute myeloid leukemia (AML)	2017	2018[c]	28% (104)	29
Tisagenlecleucel	R/R B-ALL	2017	2018	90% (105)	30
Dasatinib	CML/Ph$^+$ ALL	2017	2017	82% CCyR [CML chronic phase (CP); ref. 22]	17
Imatinib	Ph$^+$ ALL and chronic myeloid leukemia (CML)	2017	2013	70% ALL, 83% CML CP (23)	10 ALL, 14 CML
Nilotinib	CML	2018	2017	90% (24)	10
Larotrectinib	TRK fusion solid tumors	2018	2019	93% (13)	15
Entrectinib	TRK fusion solid tumors (≥12 years)	2019	2020	100% (26)	6
Tazemetostat	Epithelioid sarcoma (≥16 years)	2020	N/A	29% (106)	7
Selumetinib	Plexiform neurofibroma	2020	N/A	71% (107)	24
Selpercatinib	RET-mutant/fusion thyroid cancer (≥12 years)	2020	N/A	Not yet reported	
Rituximab	Mature B-cell lymphomas	N/A	2020	41% (108)	87

Abbreviations: CCyR, complete cytogenetic response; CR, complete response; MSI, microsatellite instability; N/A, not approved; NC, no centralized procedure when approved (approved by each individual European Union country).
[a]If no pediatric phase I in targeted population, first published phase II response rate.
[b]Dinutuximab was approved in 2015, but authorization for commercialization was then withdrawn by the company. Dinutuximab beta was approved in 2017.
[c]Only children ≥ 15 years old.

17 drugs in 25 years

Approved by FDA and/or EMA for pediatric cancer

Laetsch TW et al, Cancer Discovery, 2021

La ricerca clinica in oncologia pediatrica

Innovative Therapies for Children and adolescents with Cancer

- Network accademico attivo dal 2003
- 68 centri coinvolti in 18 nazioni (+25 laboratori)
- 9 centri in Italia

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

- Valutazione di nuovi farmaci in oncologia pediatrica
- Sviluppo di modelli di ricerca pre-clinica

➢ *Collaborazione con industrie farmaceutiche ed enti regolatori*
➢ *Collaborazione con associazioni di parenti / pazienti*

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

10 ANNIVERSARY

- *Pediatric oncologists*
- *Pharma companies*
- *Regulatory authorities*
- *Patients and parents advocates*

bring together academia, industry, advocacy and regulators to find solutions for more and better innovative therapies for children and adolescents with cancer

➢ Pediatric development should be based on drug **mechanism of action** instead of adult indication or histology

➢ **Prioritisation** should be set up to choose compounds to be evaluated or not in children

➢ **Reduce delays in starting pediatric development**

➢ **Break the 18 years dogma**

➢ **New incentives and rewards**

GdL Nuovi Farmaci AIEOP

- Valutare e promuovere studi clinici di fase precoce (I-II)
- Divulgare a tutti quali siano le risorse disponibili e accessibili
- Favorire la centralizzazione dei casi nei centri di riferimento

GdL Nuovi Farmaci AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

9 centri AIEOP coinvolti

(*Bologna, Genova, Milano, Monza, Napoli, Padova, Roma B.Gesù, Roma Gemelli, Torino*)

Changing the landscape

European Journal of Cancer 166 (2022) 145–164

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

ACCELERATE – Five years accelerating cancer drug development for children and adolescents

- Change to a **mechanism of action approach** (agnostic drugs)
- Increase access of AYAs to adult trials (18 years barrier)

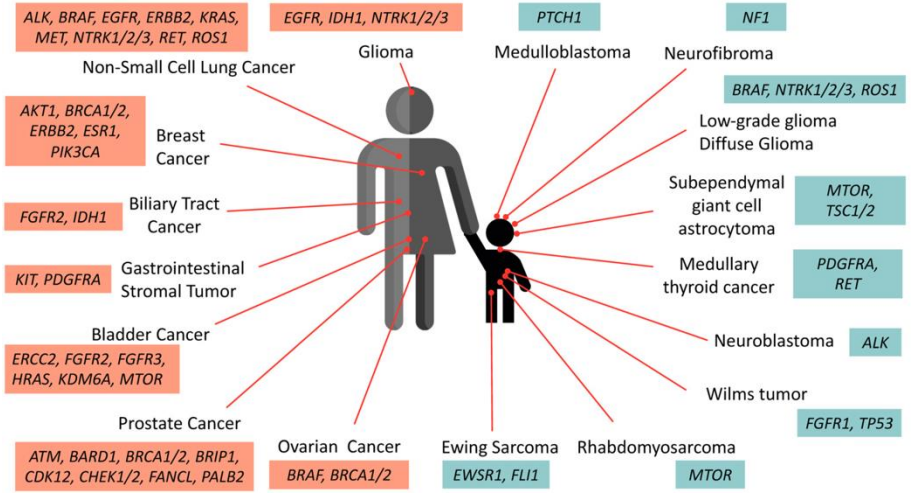
Challenges in Paediatric Oncology Drug Development 2015 and situation in 2021.

Topic	2015	2021
Drug development	Driven by the adult condition (not by science, mechanism of action or unmet need)	Change to a mechanism of action approach RACE Act in US [9], change of Class Waiver List in Europe [19]
Multi-stakeholder collaboration	Lack of true understanding and communication between the stakeholders (Industry, Academia, Regulators, Patient Advocates)	Increase in multi-stakeholder interaction, especially within ACCELERATE Paediatric Strategy Forums
Molecularly targeted therapies	Very few assessed in paediatrics and integrated into front-line therapy - BCR-ABL	Increasing inclusion in front-line therapy - ALK [56,57], BRAF [58], TRK inhibitors [59]
Immunotherapy	New and effective therapies approved for adult cancers, none for children	Blinatumomab, dinutuximab, dinutuximab beta, CAR T-Cells approved for paediatric malignancies
Early-phase trials	In Europe early phase trials delivered by ITCC increased: from one in 2007 to 12 in 2013	In Europe, 26 open studies in ITCC One multi-arm (now 15 arms) combination phase I/II platform trial (ESMART) [60]
Number of PIPs	The expected increase after change in EU regulation not materialised 17 PIPs in 2007–2013	124 PIPS in oncology after 2013 141 PIPS in oncology 2007–2021
Approved anti-cancer agents with at least one paediatric indication	9	19
PIP strategy	Multiple PIPs in very rare paediatric populations	Focused and sequential strategy for development of novel agents has been developed [31]
Access of AYAs to adult trials	PIPs for conditions in adolescents were not possible to complete (rarity in the population) Adolescents were denied access to adult clinical trials investigating innovative drugs when suffering from the same malignancy, such as metastatic melanoma	Increasing the inclusion of adolescents in adult trials and age inclusive marketing authorisation using of extrapolation [61–63]
Methodology innovation	Lack of innovative trial designs	Increasing the use of platform trial designs – ESMART [60], Pedal/EUPAL [64], GloBNHL, Paediatric MATCH [65]
Incentives	No incentives to develop drugs against specific paediatric targets	No incentives to develop drugs against specific paediatric targets

Paerson ADJ et al, EJC, 2022

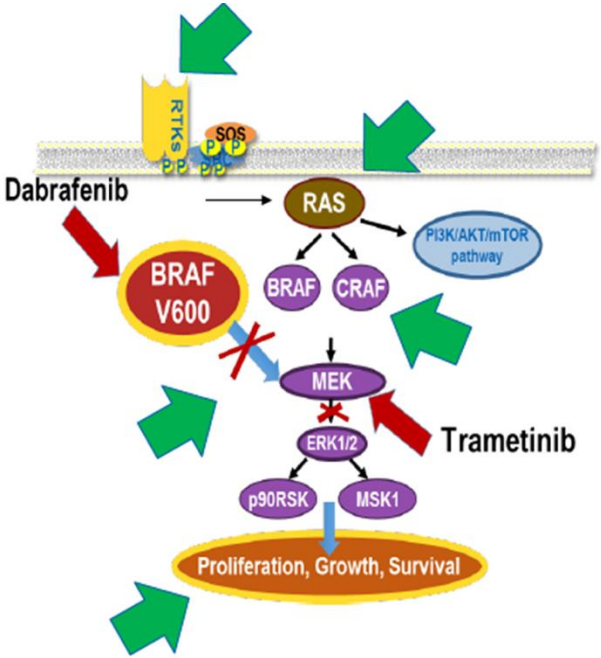
Ruolo della terapia target in oncologia pediatrica

La presenza di specifici bersagli molecolari ha cambiato dei paradigmi di trattamento



- BRAF-inibitori in tumori con mutazione di BRAFV600E (glioma, melanoma, istiocitosi a cellule di Langerhans)
- ALK-inibitori in tumori con traslocazioni di ALK (linfoma anaplastico a grandi cellule, tumore miofibroblastico infiammatorio)
- NTRK-inibitori in tumori con geni di fusione NTRK
- RET-inibitori in tumori con alterazioni del gene RET (carcinoma midollare della tiroide)

Dabrafenib + Trametinib



gliomi, melanoma, istiocitosi a cellule di Langerhans

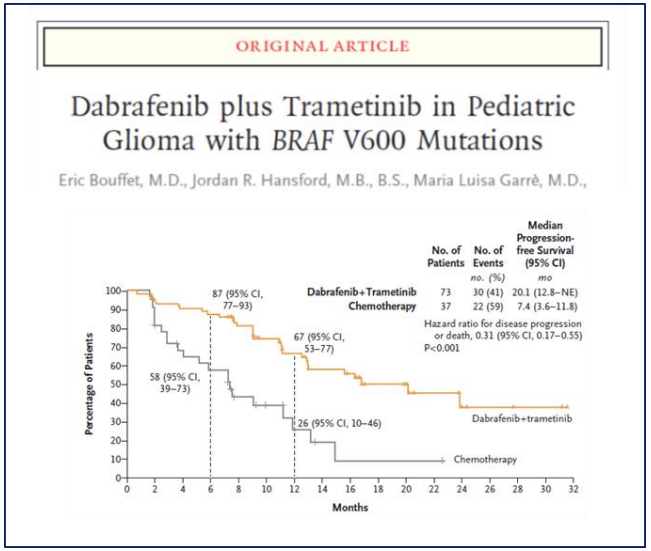
A Phase I and Pharmacokinetic Study of Oral Dabrafenib in Children and Adolescent Patients with Recurrent or Refractory *BRAF* V600 Mutation–Positive Solid Tumors

Mark W. Kieran[1], Birgit Geoerger[2], Ira J. Dunkel[3], Alberto Broniscer[4], Darren Hargrave[5], Pooja Hingorani[6], Isabelle Aerts[7], Anne-Isabelle Bertozzi[8], Kenneth J. Cohen[9], Trent R. Hummel[10], Violet Shen[11], Eric Bouffet[12], Christine A. Pratilas[9], Andrew D.J. Pearson[13], Lillian Tseng[14], Noelia Nebot[14], Steven Green[15], Mark W. Russo[14], and James A. Whitlock[12]

TMT212X2101 pediatric Phase I Trial
Dose-finding study for Trametinib (TMT) monotherapy and TMT+DRB combination

Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)

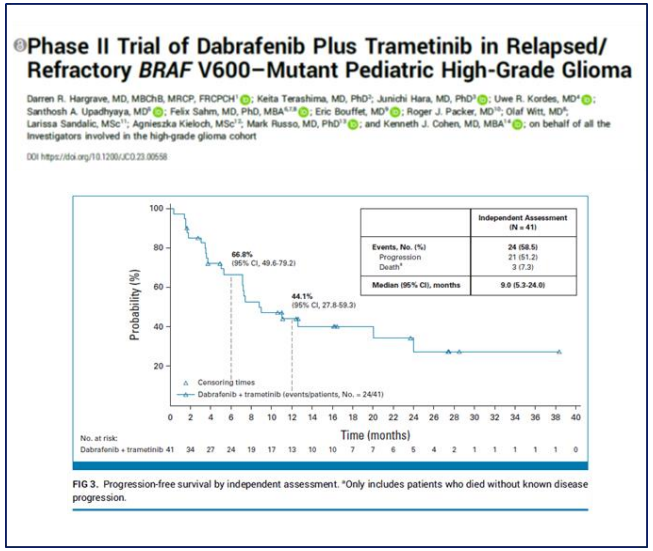
Dabrafenib + Trametinib



ORIGINAL ARTICLE

Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations

Eric Bouffet, M.D., Jordan R. Hansford, M.B., B.S., Maria Luisa Garrè, M.D.,



Phase II Trial of Dabrafenib Plus Trametinib in Relapsed/ Refractory *BRAF* V600–Mutant Pediatric High-Grade Glioma

Darren R. Hargrave, MD, MBChB, MRCP, FRCPCH[1]; Keita Terashima, MD, PhD[2]; Junichi Hara, MD, PhD[3]; Uwe R. Kordes, MD[4]; Santhosh A. Upadhyaya, MD[5]; Felix Sahm, MD, PhD, MBA[6,7,8]; Eric Bouffet, MD[9]; Roger J. Packer, MD[10]; Olaf Witt, MD[6]; Larissa Sandalic, MSc[11]; Agnieszka Kieloch, MSc[12]; Mark Russo, MD, PhD[13]; and Kenneth J. Cohen, MD, MBA[14]; on behalf of all the Investigators involved in the high-grade glioma cohort

DOI https://doi.org/10.1200/JCO.23.00558

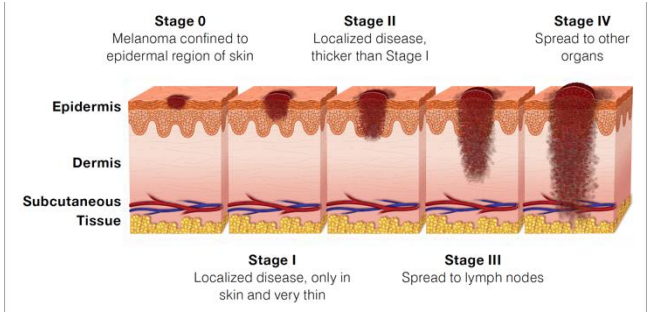
FIG 3. Progression-free survival by independent assessment. *Only includes patients who died without known disease progression.

Indicazione AIFA - maggio 2024

FINLEE (trametinib) *polvere per soluzione orale*
+
SPEXOTRAS (dabrafenib) *compresse dispersibili*

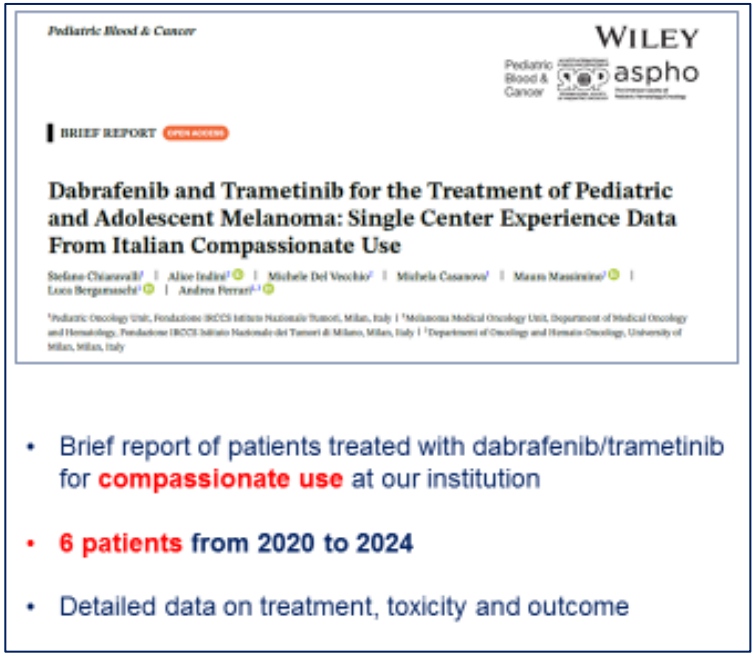
- pazienti pediatrici di età ≥ 1 anno affetti da **glioma a basso grado (LGG)** con una mutazione BRAF V600E **che necessitano di una terapia sistemica**
- pazienti pediatrici di età ≥ 1 anno affetti **da glioma ad alto grado (HGG)** con una mutazione BRAF V600E **che hanno ricevuto almeno un precedente trattamento** radioterapico e/o chemioterapico

Dabrafenib + Trametinib



On **March 26, 2026**, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the **extension of the marketing authorization for Tafinlar (dabrafenib) and Mekinist (trametinib)** to include the treatment of **children and adolescents from 12 years of age with BRAF V600E-mutated melanoma**.

This recommendation covers both **unresectable or metastatic melanoma** and **adjuvant treatment** following complete surgical resection.



Pediatric Blood & Cancer

WILEY

Pediatric Blood & Cancer aspho

BRIEF REPORT OPEN ACCESS

Dabrafenib and Trametinib for the Treatment of Pediatric and Adolescent Melanoma: Single Center Experience Data From Italian Compassionate Use

- Brief report of patients treated with dabrafenib/trametinib for **compassionate use** at our institution
- **6 patients from 2020 to 2024**
- Detailed data on treatment, toxicity and outcome

ALK aberrations in pediatric patients

Translocations and Rearrangements

- **ALCL:** ~ 90% harbor *ALK* translocations with NPM1 as the fusion partner in ~75%
- **Inflammatory myofibroblastic tumor (IMT):** 45–65% carry *ALK* rearrangements

Mutations and Amplifications

- **Neuroblastoma:** 8–10% carry activating point mutations; ~2% carry ALK gene amplification; the frequency increases at relapse, where ALK mutations have been reported in ~17% of patients.

Expression

- **Rhabdomyosarcoma (RMS):** ALK protein is expressed in about 70% of alveolar RMS cases, typically without an *ALK* mutation. Other ALK abnormalities reported include ALK gene copy number gain, rare point mutations and whole exon deletions.

Crizotinib

Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study

79 patients from 2009 to 2012 with median age 10 years

Crizotinib was well tolerated with a **RP2D of 280 mg/m² twice daily**

Overall response rate: 18% (14/79: 9 CR, 5 PR)

- *ALCL (RR): 89% (8/9)*
- *IMT (RR): 43% (3/7)*
- *NBL ALK+ (RR): 9% (1/11)*

Lancet Oncol, 2013

Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study

Yael P. Mossé, Stephan D. Voss, Megan S. Lim, Delphine Rolland, Charles G. Minard, Elizabeth Fox, Peter Adamson, Keith Wilner, Susan M. Blaney, and Brenda J. Weigel

40 patients with ALCL or IMT ALK+ from 2009 to 2015

Table 2. Clinical Activity in Patients Treated With Crizotinib

Outcome	ALCL165 (n = 6)	ALCL280 (n = 20)	IMT (n = 14)
Best overall response			
Complete response	5 (83)	16 (80)	5 (36)
Partial response	0	2 (10)	7 (50)
Stable disease	1 (17)	2 (10)	2 (14)
Progressive disease	0	0	0
Therapy duration, years, median (95% CI)	2.79 (0.31 to n/a)	0.4 (0.18 to 1.0)	1.63 (0.55 to 2.30)
Time to first PR/CR, days, median (95% CI)	26.5 (24 to n/a)	27 (25 to 29)	28.5 (27 to 134)

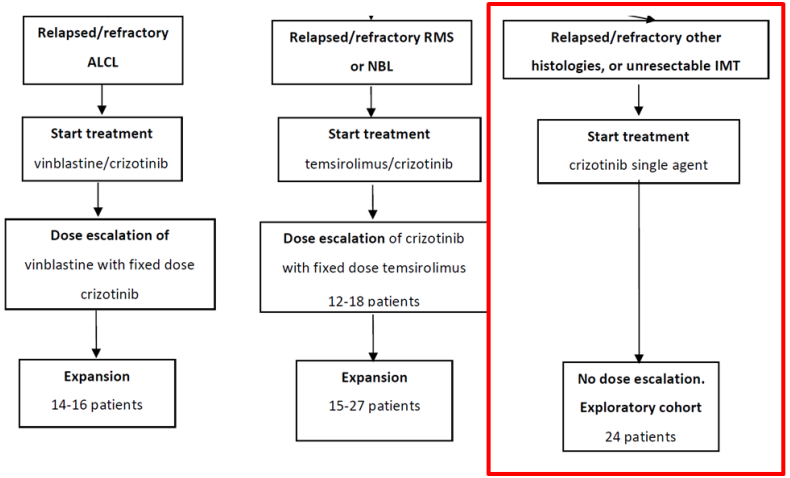
ALCL (RR): 88% (23/26)
IMT (RR): 86% (12/14)

JCO, 2017

Crizotinib

A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies (CRISP study)

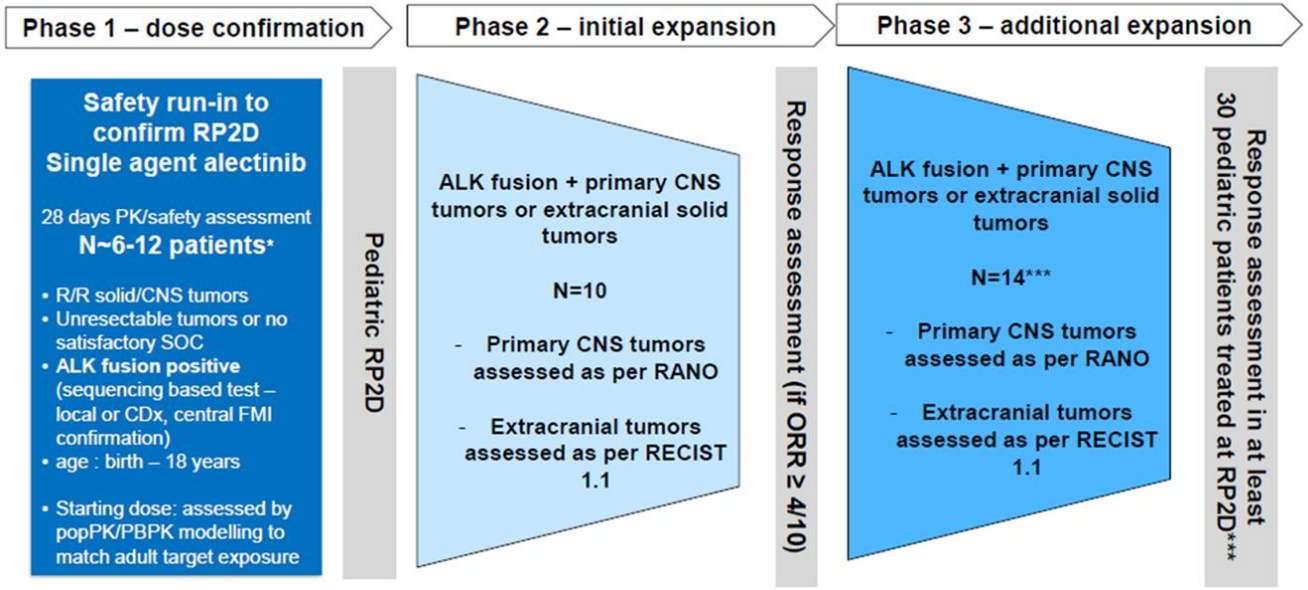
Crizotinib indicated for the treatment of **patients ≥1 year of age** and young adults with relapsed or refractory ALK-positive anaplastic large cell lymphoma (**ALCL**) or ALK-positive unresectable inflammatory myofibroblastic tumour (**IMT**)



***Pediatric formulation**: granules in capsules for opening*

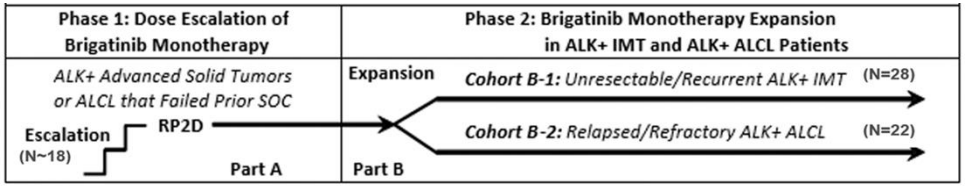
Alectinib

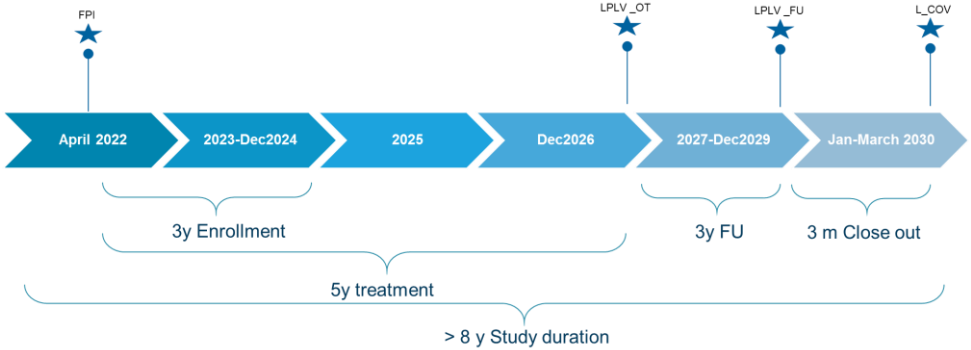
A PHASE I/II, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF ALECTINIB IN PEDIATRIC PATIENTS WITH ALK FUSION-POSITIVE SOLID OR CNS TUMORS FOR WHOM PRIOR TREATMENT HAS PROVEN TO BE INEFFECTIVE OR FOR WHOM THERE IS NO CURATIVE STANDARD TREATMENT AVAILABLE



Brigatinib

A Phase I/II study of Brigatinib in pediatric and young adult patients with ALK+ Anaplastic Large Cell Lymphoma, Inflammatory Myofibroblastic Tumors or other solid tumors





Lorlatinib

nature medicine

Article https://doi.org/10.1038/s41591-023-02297-5

Lorlatinib with or without chemotherapy in ALK-driven refractory/relapsed neuroblastoma: phase 1 trial results

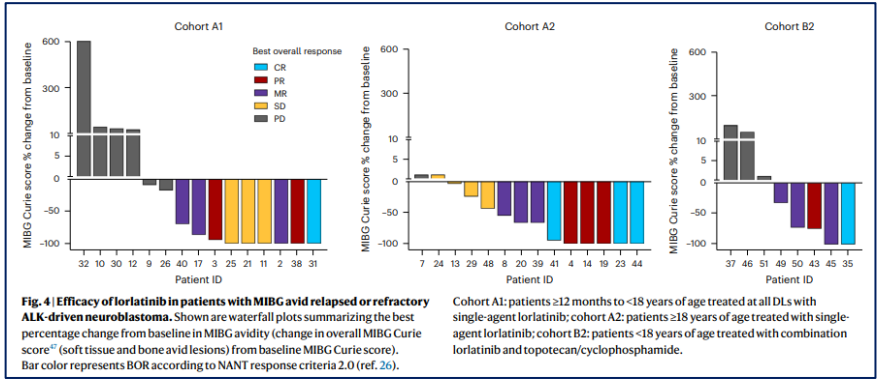


Fig. 4 | Efficacy of lorlatinib in patients with MIBG avid relapsed or refractory ALK-driven neuroblastoma. Shown are waterfall plots summarizing the best percentage change from baseline in MIBG avidity (change in overall MIBG Curie score[47] (soft tissue and bone avid lesions) from baseline MIBG Curie score). Bar color represents BOR according to NANT response criteria 2.0 (ref. 26). Cohort A1: patients ≥12 months to <18 years of age treated at all DLs with single-agent lorlatinib; cohort A2: patients ≥18 years of age treated with single-agent lorlatinib; cohort B2: patients <18 years of age treated with combination lorlatinib and topotecan/cyclophosphamide.

3+3 dose-escalation design

Cohort A1	Cohort A2	Cohort B2* (chemotherapy combination)
≥12 months to <18 years	≥18 years	≥12 months to <18 years
Lorlatinib, DL1–DL5 (45, 60, 75, 95, 115) mg/m²/dose QD	Lorlatinib 100 mg, 150 mg QD	Lorlatinib, DL4 & DL5 (95, 115) mg/m²/dose QD +Topo/Cy#

Cohort A1 and A2. Treatment schema

Course 1	Course 2
Days 1–28	Days 1–28*
Lorlatinib PO Daily →	

- DLT evaluation through course 1; CNS DLT evaluation through course 2
- *Disease evaluations: Courses 2,4,6, every 4th course

Cohort B2. Treatment schema for one course

Week 1							Week 2	Week 3	Week 4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8–14	Days 15–21	Days 22–28*
Lorlatinib PO Daily →									
Cy	Cy	Cy	Cy	Cy					
Topo	Topo	Topo	Topo	Topo	MGF				

- DLT evaluation: Course 1
- *Disease evaluations: Courses 2,4,6, every 4th course

- The RP2D of lorlatinib with and without chemotherapy in children was 115 mg/sqm
- single-agent response rate (RR) for <18 years: 30%; for ≥18 years: 67%
- chemotherapy combination RR in <18 years: 63%
- 48% of responders achieved MIBG complete responses

Goldsmith KC et al, Nat Med, 2023

Neladalkib (NVL-655)

***4th-generation ALK inhibitor** designed to overcome resistance to earlier-generation therapies like lorlatinib*

ALKOVE-1

A Phase 1/2 Study of the Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor NVL-655 in Patients with Advanced NSCLC and Other Solid Tumors

Phase 1

ALK+ Solid Tumors [1]

BOIN Dose Escalation (N = 70)

- 200 mg QD [2]
- 150 mg QD
- 100 mg QD
- 50 mg QD
- 25 mg QD
- 15 mg QD

Dose Expansion at Candidate RP2Ds (up to n = 40 each) [3]

Safety, Tolerability, MTD & RP2D

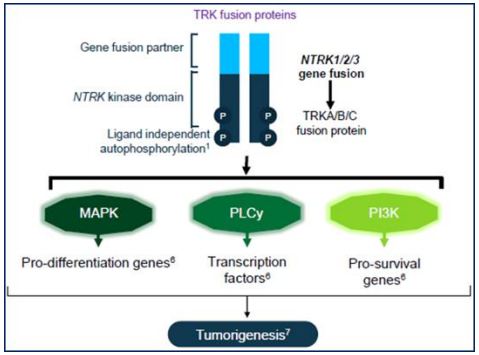
Phase 2 (N ≈ 700)

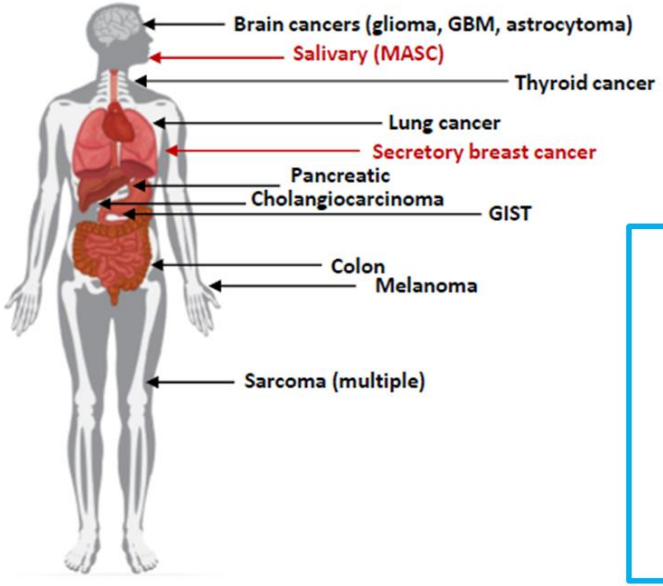
COHORT	N [4]	TUMOR TYPE	PRIOR ALK TKI [5]	PRIOR CHEMO and/or IO
2a	92	ALK fusion+ NSCLC	1 prior 2nd generation (ceritinib, alectinib, or brigatinib)	0 – 2 lines
2b	137	ALK fusion+ NSCLC	2 – 3 prior ALK TKIs (crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib [6])	0 – 2 lines
2c	20	ALK fusion+ NSCLC	Lorlatinib as the only prior ALK TKI	≤ 1 [7]
2d	20	ALK fusion+ NSCLC	ALK TKI naive	≤ 1
2e	40	ALK fusion+ NSCLC	Any (not eligible for other cohorts)	Any
2f	50	Other ALK+ solid tumors	≥ 1 prior systemic therapy (or for whom no satisfactory standard therapy exists)	Any

Efficacy endpoints include ORR (primary), DOR, measures of intracranial activity

Phase 2 Cohort 2f only: Age ≥12 years and weight >40 kg

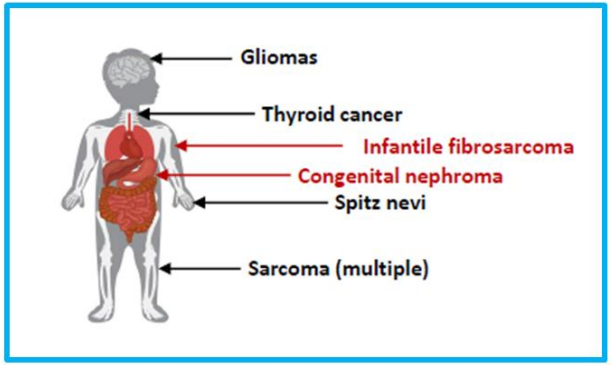
NTRK fusions and cancer





Common cancer with low TRK fusion frequency

Rare cancer with high TRK fusion frequency



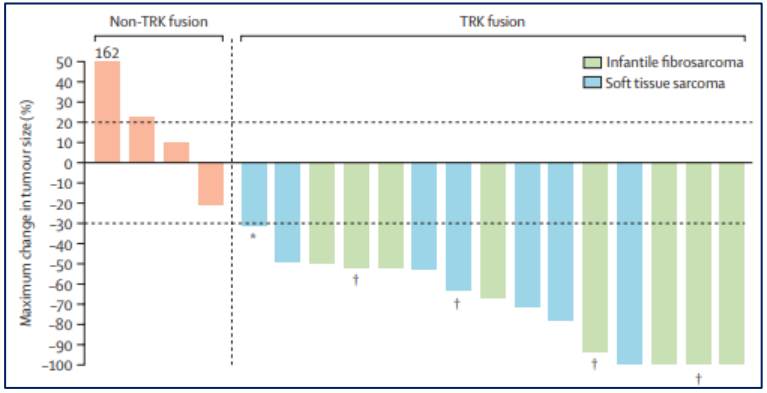
NTRK fusions identified in several pediatric and adult neoplasms

Larotrectinib

Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Theodore W Laetsch*, Steven G DuBois*, Leo Mascarenhas, Brian Turpin, Noah Federman, Catherine M Albert, Ramamoorthy Nagasubramanian, Jessica L Davis, Erin Rudzinski, Angela M Feraca, Brian B Tuch, Kevin T Ebata, Mark Reynolds, Steven Smith, Scott Cruickshank, Michael C Cox, Alberto S Pappo*, Douglas S Hawkins*

www.thelancet.com/oncology Published online March 29, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30119-0



Meeting Abstract | 2022 ASCO Annual Meeting I

PEDIATRIC ONCOLOGY

Efficacy and safety of larotrectinib in pediatric patients with tropomyosin receptor kinase (TRK) fusion-positive cancer: An expanded dataset.

Leo Mascarenhas, Cornelis Martinus van Tilburg, Francois Doz, C. Michel Zwaan, Catherine M. Albert, Claudia Blattman, Birgit Geoerger, Steven G. DuBois, Noah Federman, Ramamoorthy Nagasubramanian, Alberto S. Pappo, Tanya Carens Watt, Ricarda Norenberg, Marc Mandoche Fellous, Esther A. De La Cuesta, Theodore Willis Laetsch, Rui-hua Xu

94 pediatric patients (< 18 years) with non-CNS TRK fusion-positive cancer in larotrectinib clinical trials (NCT02637687, NCT02576431)

- infantile fibrosarcoma (52%), other soft tissue sarcoma (40%), congenital mesoblastic nephroma (2%), thyroid cancer (2%), bone sarcoma (1%), breast cancer (1%), and melanoma (1%)

- **ORR:** 84% (CR 38%, PR 46%, SD 12% PD 2%, Unknown 2%)
- Median time to response: 1.8 months
- **Median duration of response: 43.3 months** (median follow-up 26.0 months)
- **Median PFS and OS:** 37.4 months (95% CI 22–NE) and not reached, respectively
- **36-month OS rate:** 93% (95% CI 86–99).
- Treatment duration ranged from 1+ to 63+ months

- **Treatment-related adverse events** occurred in 81% of pts (23% G1, 28% G2, 25% G3, and 5% G4).
- The most common TRAE was increased aspartate aminotransferase (31 pts [33%])
- 4% discontinued treatment due to TRAEs

Pediatric protocol active since 2015

Entrectinib

A PHASE 1/2, OPEN-LABEL, DOSE-ESCALATION AND EXPANSION STUDY OF ENTRECTINIB (RXDX-101) IN PEDIATRICS AND YOUNG ADULTS WITH NO CURATIVE FIRST-LINE TREATMENT OPTION OR RECURRENT/REFRACTORY SOLID TUMORS AND PRIMARY CNS TUMORS

Pediatric and adolescent patients
Total enrolled (n=29); data cut-off October 31, 2018

Eligibility criteria
- Birth–21 years
- Relapsed or refractory solid tumors (including primary CNS tumors)
- Karnofsky or Lansky score ≥60%, minimum life expectancy ≥4 weeks
- Measurable or evaluable disease (dose escalation), measurable disease (dose expansion)
- With or without target molecular aberrations in *NTRK1/2/3*, *ROS1* or *ALK*

Treatment
- Oral administration
- QD, 28-day cycles

Primary endpoints*
- MTD, RP2D

Key secondary endpoints
- Safety and tolerability
- Plasma PK: C_{max}, CSS, $T_{1/2}$, AUC
- Anti-tumor activity: ORR, PFS

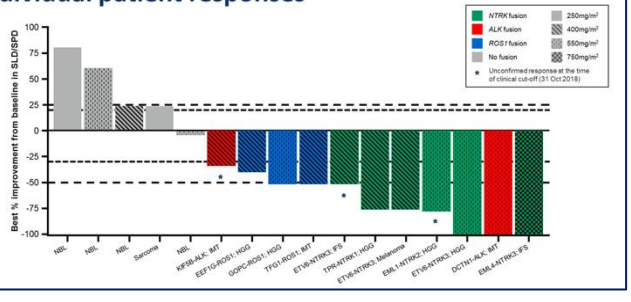
Dose-finding phase 1 (N=16) in patients with relapsed or refractory solid tumors
Dose level 250–750mg/m²
Sequential assignment to escalating doses of entrectinib (3+3 design), initially dosed by BSA

250mg/m² (n=3) | 400mg/m² (n=3) | 550mg/m² (n=7) | 750mg/m² (n=3)

Basket trial phase 1b (N=13)
Dose level 550mg/m² (n=7) OR 400mg/m² in patients unable to swallow intact capsules (n=6)

Primary CNS tumors (n=6) | Neuroblastoma (n=3) | Extracranial solid tumors (n=4)

Entrectinib in pediatric solid tumors: individual patient responses



Measureable and durable responses in CNS tumors

NTRK inhibitors – regulatory approval

Larotrectinib

Approved:
FDA 2018, Brazil, Canada, EMA 2019

Indication: For the treatment of patients with solid tumours harbouring NTRK fusions in paediatric or adult patients

Dose: 25-mg or 100-mg oral capsule or 20-mg/mL oral solution

- Adults and children with BSA ≥1.0m^2: 100 mg orally BID
- Children with BSA ≤1.0m^2 : 100 mg/m^2 orally BID

Entrectinib

Approved: FDA 2019 and Japan 2019

Indication: For the treatment of NTRK fusion-positive advanced or recurrent solid tumours in adult patients and paediatric patients aged ≥12 years old

Dose: 100-mg and 200-mg oral capsule

- Adults: 600 mg orally once daily
- Children: Recommended dose based on BSA

Repotrectinib

inhibitor of tyrosine-protein kinase ROS1 and of the tropomyosin receptor tyrosine kinases (TRKs)

Experience Overview : Trident-1 study

ROS1+ ADVANCED NSCLC				*NTRK*+ ADVANCED SOLID TUMORS	
EXP-1	EXP-2	EXP-3	EXP-4	EXP-5	EXP-6
ROS1 TKI-naive	1 prior ROS1 TKI AND 1 platinum-based chemotherapy	2 prior ROS1 TKIs AND No prior chemotherapy	1 prior ROS1 TKI AND No prior chemotherapy	TRK TKI-naive	TRK TKI pretreated
(n=55)	(n=60)	(n=40)	(n=60)	(n=55)	(n=40)
cORR 79% (n=71) (95% CI: 68, 88)	cORR 42% (n=26) (95% CI: 23, 63)	cORR 28% (n=18) (95% CI: 10, 54)	cORR 36% (n=56) (95% CI: 23, 50)	cORR 41% (n=17) (95% CI: 18, 67)	cORR 48% (n=23) (95% CI: 27, 69)
	SFM G2032R cORR 59% (n=17) (95% CI: 33, 82)				SFMs cORR 62% (n=13) (95% CI: 32, 86)

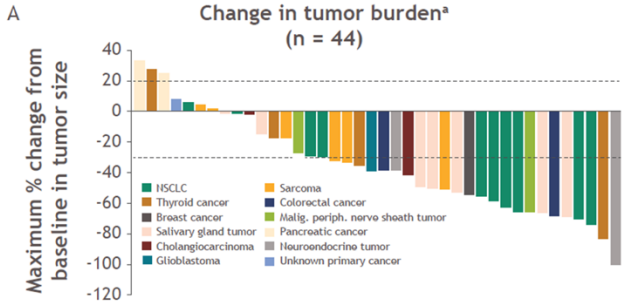
Phase 2 Primary Objective
- cORR by BICR in each expansion cohort

Phase 2 Secondary Objectives
- DOR, PFS, and OS
- IC-ORR and CNS-PFS

Note: EXP-1, EXP-2, EXP-3 and EXP-4 data reported Apr-2022. Data pooled across the Phase 1 and 2 portions of TRIDENT-1 with a data cutoff of 11-Feb-2022 with responses confirmed per RECIST1.1 and assessed by BICR. Pooled Phase 1 and Phase 2 patients included those who received at least 1 dose of repotrectinib with at least 4 months of follow-up, and most responders had at least 6 months of DOR follow-up. EXP-5 and EXP-6 data presented at the 2021 AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics. Phase 2 data cutoff date of 26-Aug-2021 with responses confirmed by physician assessment. Data pooled from the Phase 1 portion (treated at or above the Phase 2 dose) with patients from the Phase 2 portion who had at least one post-baseline evaluable scan or were off treatment prior to first post-baseline scan. EXP-6 data updated since pre-recorded presentations at the AACR-NCI-EORTC conference. Phase 1 data cutoff of 22-Jul-2019 with responses confirmed per RECIST1.1 and assessed by BICR.
BICR: blinded independent central review; CI: confidence interval; cORR: confirmed objective response rate; EXP: expansion; NSCLC: non-small cell lung cancer; SFM: solvent front mutation; TKI: tyrosine kinase inhibitor

In **November 2023** the U.S. Food ad Drug Administration (FDA) approved ***Augtyro***™ **(repotrectinib)** for the treatment of adult patients with **locally advanced or metastatic *ROS1*-positive NSCLC**

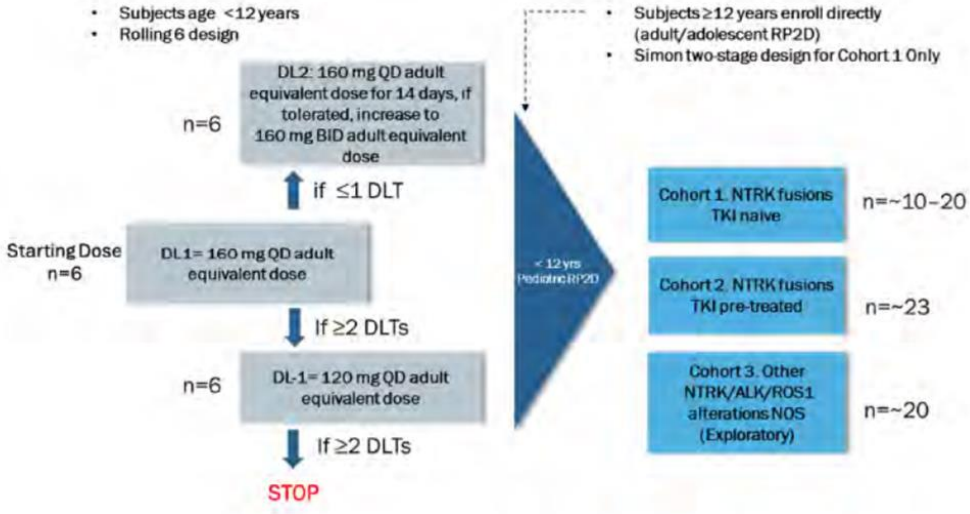
Efficacy in TRK TKI-pretreated patients with *NTRK*+ advanced solid tumors



TRK TKI-pretreated (EXP-6) (n = 44)	
ORR by investigator[a], % (95% CI)	43.2 (28.3–59.0)
CR, n (%)	1 (2.3)
PR, n (%)	18 (40.9)
CBR per investigator[b], % (95% CI)	75 (59.7–86.8)
Duration of response, range, mo	1.05+-17.54
Median time to response, mo (range)	1.87 (1.7–3.7)

Repotrectinib

TPX-0005-07 Phase 1/2 Pediatric Study Schema

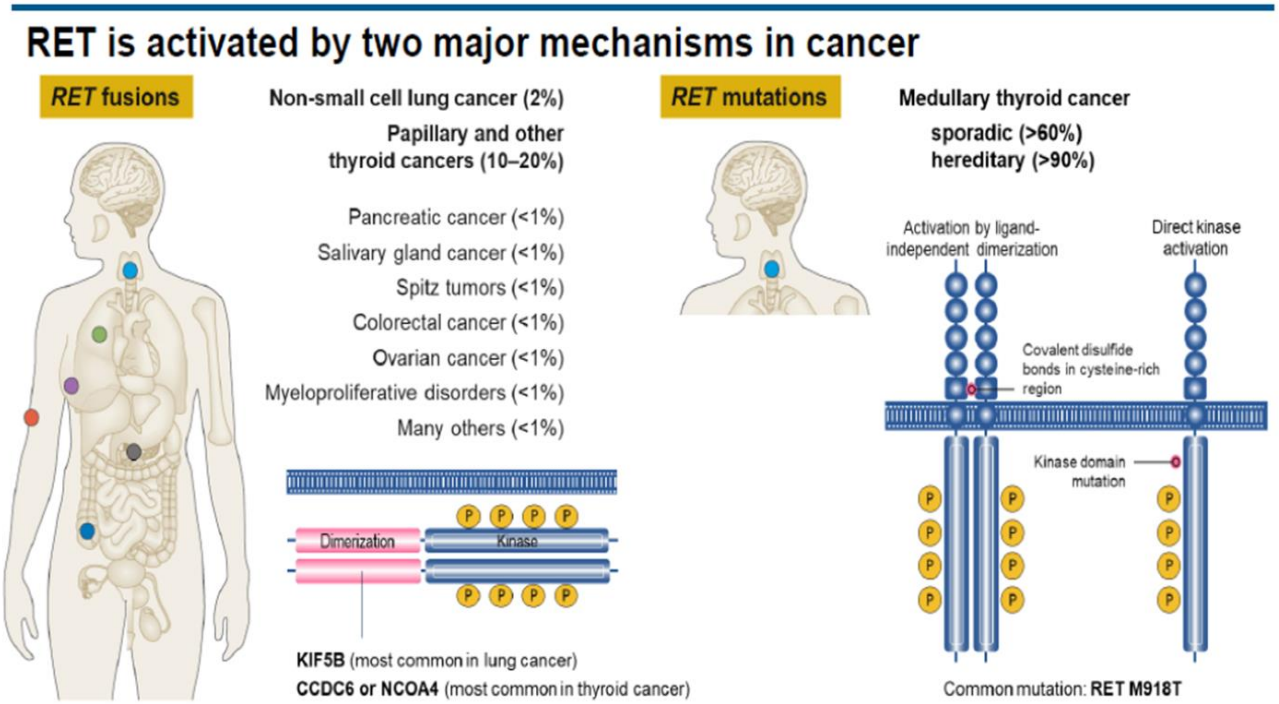


Phase 1:
Enrollment complete
Phase 2:
[1]The EU will not participate in Cohort 1.

Cohort 2: Subjects with NTRK+ fusions that are TRK TKI pretreated with 1 or 2 prior TKIs will be enrolled into cohort 2 once there is confirmation of measurable disease.

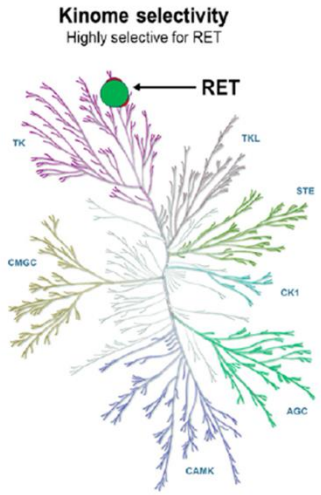
Cohort 3:
Subjects with ROS1 fusions with measurable disease (BICR confirmation is not required)

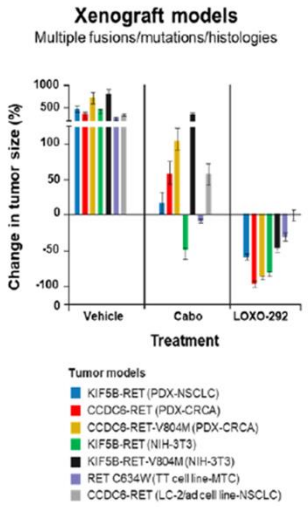
RET aberrations in cancer



Selpercatinib

Inibitore di RET potente e selettivo



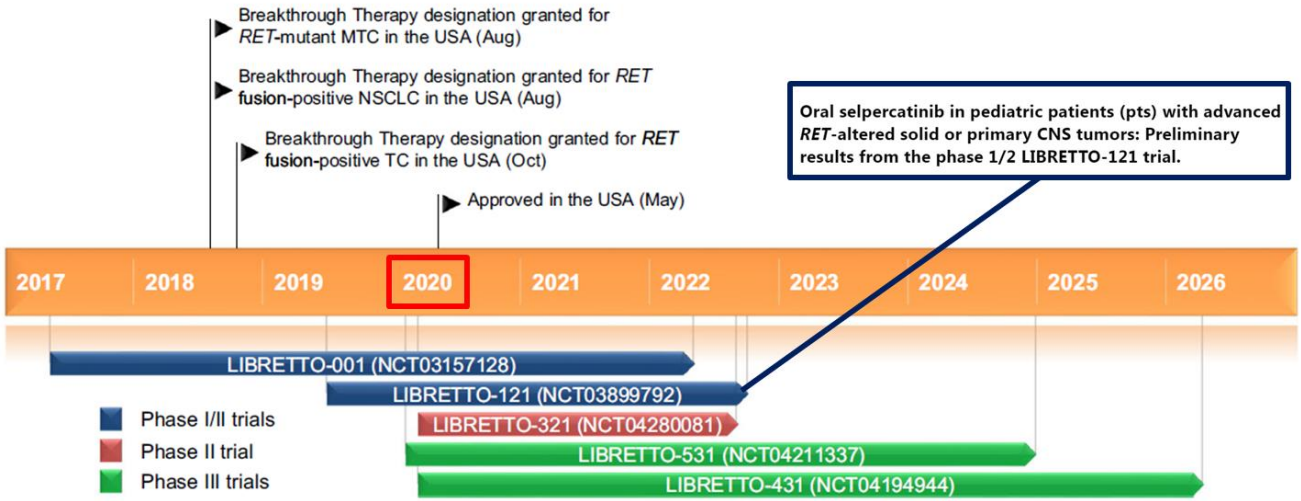


Protocollo LIBRETTO-121

- **Studio di fase I/II multicentrico condotto in pazienti pediatrici con tumori solidi o del SNC in stadio avanzato con alterazione di *RET***
- Età compresa tra ≥6 mesi e ≤21 anni (≥12 anni in UE e Canada)
- Somministrazione iniziata a 92 mg/m^2 BID equivalente alla dose negli adulti di 160 mg BID
- RP2D confermata separatamente per pazienti di età < 2 anni e ≥ 2 anni
- Endpoint primari: MTD/RP2D (fase 1), ORR (fase 2)

Arruolamento iniziato a febbraio 2019
RP2D di **92 mg/mq BID approvata a dicembre 2019** (età >2 anni)

Selpercatinib

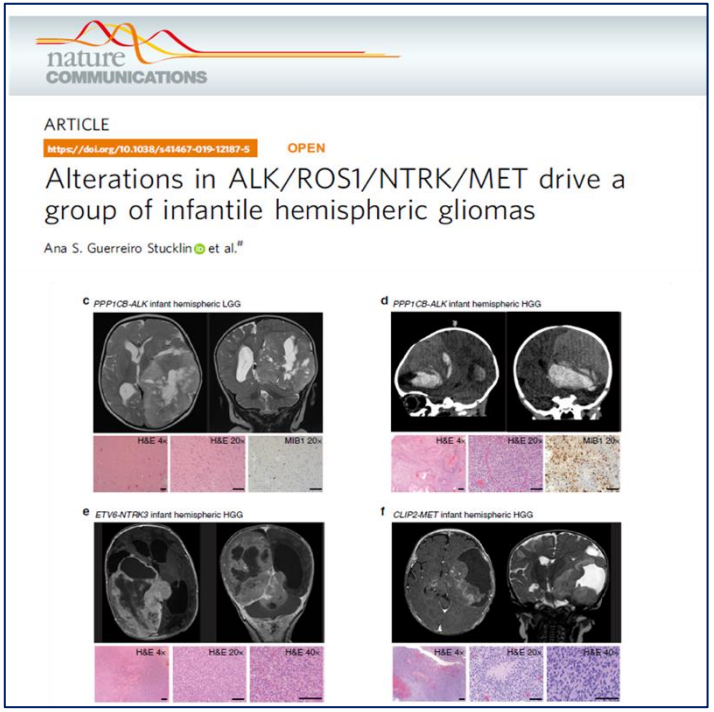


2020

- adult patients with metastatic RET fusion-positive NSCLC
- **adult and paediatric patients ≥12 years** of age with advanced or metastatic **RET-mutant medullary thyroid cancer** who require systemic therapy
- **adult and paediatric patients ≥12 years** of age with advanced or metastatic **RET fusion-positive thyroid cancer** who require systemic therapy

Ricerca di alterazioni molecolari nei tumori pediatrici

- Ricercare target molecolari nei tumori pediatrici vale la pena
- Possibilità di individuare driver rilevanti per la malattia
- Potenziale grande beneficio da trattamenti mirati anche in malattie a cattiva prognosi



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-12187-5 OPEN

Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas

Ana S. Guerreiro Stucklin et al.#

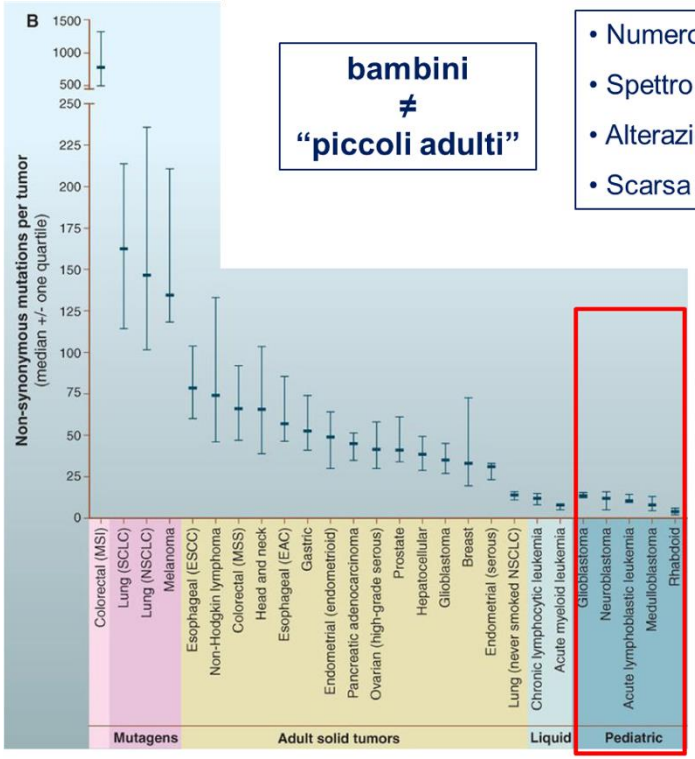
c *PPP1CB-ALK* infant hemispheric LGG

d *PPP1CB-ALK* infant hemispheric HGG

e *ETV6-NTRK3* infant hemispheric HGG

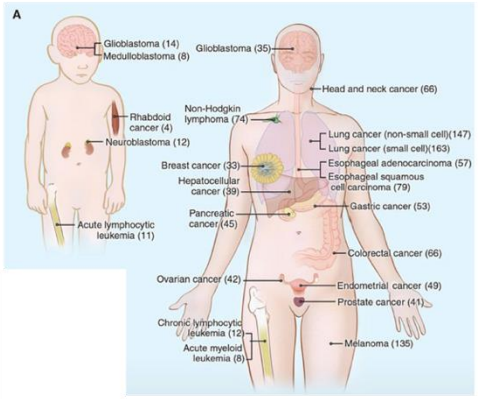
f *CLIP2-MET* infant hemispheric HGG

Pediatric cancer genome landscape



bambini
≠
"piccoli adulti"

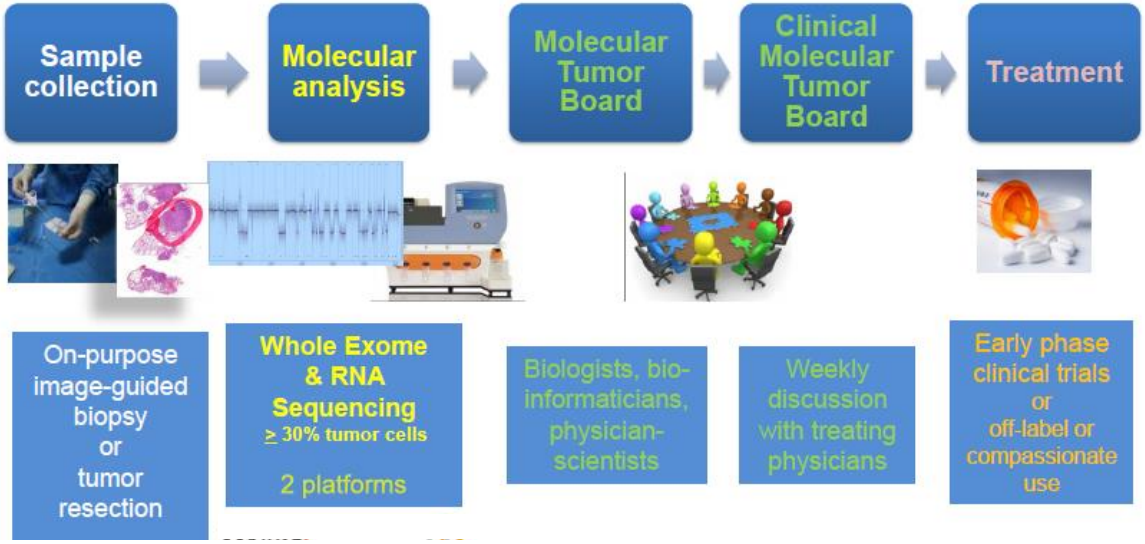
- Numero inferiore di casi
- Spettro di patologie differente
- Alterazioni genetiche diverse e meno frequenti
- Scarsa conoscenza di target specifici



Vogelstein et al. Science 2013

Precision medicine trials

Studi prospettici con l'obbiettivo di **stratificare** le terapie target in relazione al **profilo molecolare** dei tumori



ANALISI PRIMARIE

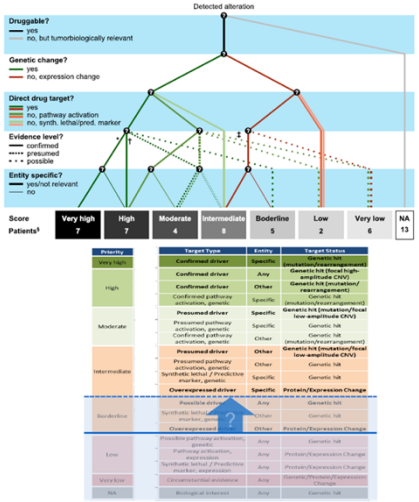
- **Whole Exome Sequencing (WES)** → mutazioni SNV, amplificazioni
- **RNA sequencing** → trascritti di fusione, varianti di splicing
- Confronto tra DNA/RNA tumorale e DNA costituzionale

ANALISI ESPLORATIVE

- Profilo di metilazione
- Espressione di miRNA
- Marker immunologici e di immunomodulazione
- *Modelli in vitro / in vivo* → *linee cellulari, PDX murini*

Precision medicine trials

Stratificazione delle alterazioni / target identificati



Ready for routine use:
NPM1/ALK , KIAA1549-BRAF, ETV6-NTRK3, KANK2/NTRK2, CCDC6-RET fusions; BRAF p.V600E, PTCH1, NF1 mutations

Investigational:
CDK4 ampli, CDKN2A/B del, PI3KCA, PTEN loss, FGFR ampli/mut, MYC ampli, ATR, ATM mut, SMARCA1...

Hypothetical target:
Histone mut, CNA gains, TP53 mut?

Resistance mutations:
SMO p.I408V, NTRK3 p.G623R

Oncogenic without level of evidence:
TP53 mut?, VUS, subclonal events

Oncogenic not targetable:
EWS/FLI1, PAX/FOXO1

"actionable" genetic alterations

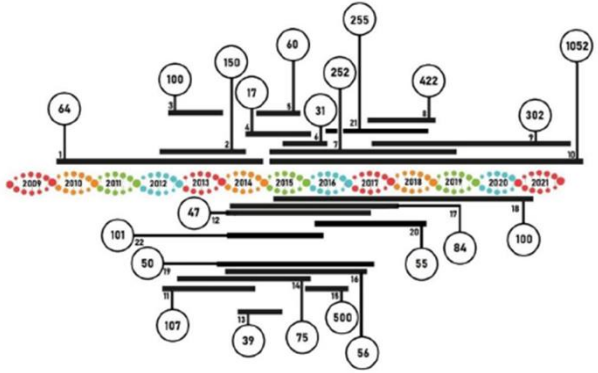
Somministrazione di una terapia target

- Trials clinici di fase I-II
- Basket trials
- Farmaci ad uso compassionevole
- Farmaci off-label

Pediatric molecular profiling trials

PROGRAM NAME	COUNTRY	REFERENCE	PERIOD	PTS INCLUDED
ClinOmics	USA	Chang W, 2016	2010-2014	64
Peds-MiOncoSeq	USA	Mody RJ, 2016	2012-2014	102
BASIC3	USA	Parsons DW, 2016	2012-2014	150
iCAT	USA	Janeway K, 2016	2012-2013	100
MOSCATO-01 (ped)	France	Harttrampf AC, 2017	2012-2016	75
ProfiLER (ped)	France	Benezech S, 2020	2013-2017	50
PIPseq	USA	Oberg JA, 2016	2014-2016	107
TRICEPS	Canada	Khater F, 2019	2014-2018	84
PMTB	USA	Ortiz MV, 2016	2014-2015	39
MMB	France	Pincez T, 2017	2014-2015	60
INFORM	Germany	Van Tilburg CM, 2021	2015-2019	1051
Zero Childhood	Australia	Wong M, 2020	2015-2019	252
MAPPYACTS	France, Italy, Ireland, Spain	Berlanga P, 2022	2016-2020	787
SMC	Korea	Lee JW, 2019	2016-2018	55
SMPAEDS	UK	George SL, 2019	2016-2019	255
iTHER	Netherlands	Langenberg KPS, 2022	2017-2021	302
Pediatric MATCH	USA	Parsons DW, 2022	2017-2020	1111
KiCS	Canada	Villani A, 2022	2016-2020	359
GAIN/iCAT2	USA	Church AJ, 2022	2015-2018	389
G4K	USA	Newman S, 2021	2015-2017	309

5700 pazienti profilati in 20 trials in 10 anni



- Profilo molecolare completo: 80-100%
- Tempo mediano prelievo-risultato: 13-61 giorni
- Alterazioni “actionable”: 23-100%
- Mutazioni germinali costitutive: 6-35%
- **Somministrazione di terapia target: 2-58%**

MAPPYACTS trial (ITCC-056)

Molecular **P**rofiling for **P**ediatric and **Y**oung **A**dult **C**ancer **T**reatment **S**tratification

Studio prospettico internazionale di medicina di precisione

Attivo da Feb 2016 a Lug 2020:

- *Francia*
- ***Italia***
- *Irlanda*
- *Spagna, Israele*

Arruolamento: **787 pazienti** *(in 18 centri)*

- neoplasia solida o ematologica refrattaria o recidivata
- età <18 anni alla prima diagnosi
- possibilità di prelievo di tessuto neoplastico

Il **30%** dei pazienti con potenziale actionable target ha ricevuto almeno un **trattamento basato sul profilo molecolare del proprio tumore** suggerito nel CMTB (range 1-4)

ORR: 17% **SD: 25%** **DCR: 41%**

*11% - **ready for routine use***	***ORR: 38%***
80% - investigational	*ORR: 14%*
9% - hypothetical	*ORR: 10%*

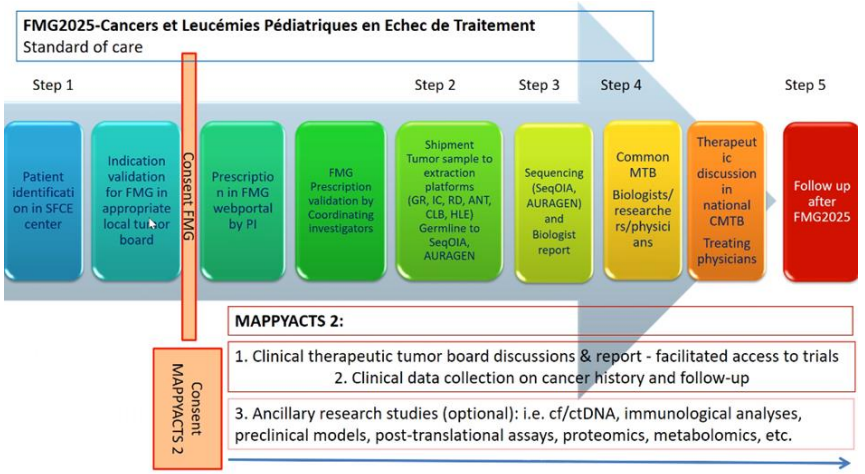
56% (68 pts) trattati in **studi di fase I/II** → **72%** (49 pts) **studio AcSè-ESMART**

Berlanga et al. Cancer Discovery 2022

MAPPYACTS 2 (ITCC-112)

MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification 2

- **Coordinating Investigator:** Dr Birgit Geoerger
- **Co-sponsors:** Spain, Italy, Ireland, Denmark, Lithuania
- 30 centers in France and 20-25 centers in other countries
- Study duration: 8 years (5 years + 3 years of follow-up)
- **Recruitment goal:** 500 patients / year (2000-2500 in 5 years)



- provide **clinical therapeutic recommendations according to the molecular profile** of a malignancy
- set up a **molecular and comprehensive clinical database** of patients with relapsed or refractory pediatric malignancies
- collect the **follow-up data** on treatment and patients' outcome, in order to determine the outcome of the program in regard to benefit to the patient, all the patients and to health care
- **central link to interventional study platforms and international precision medicine programs**
- **ancillary research studies** that lead to improved treatment and outcome for children with advanced malignancies

Programmi di sequenziamento molecolare in Italia

INT-per-Kids

MEDICINA DI PRECISIONE PER TUMORI PEDIATRICI
studio clinico pilota, monocentrico, prospettico, finalizzato a stratificare terapie mirate sulla base della profilo molecolare di tumori pediatrici recidivanti o refrattari

- Tumori solidi recidivati / refrattari
- *Milano*

PREME
PeRsonalized mEdicine: developMEnt of precision cancer therapies

- Neuroblastomi recidivati / refrattari
- *Genova, Napoli*

IIGM Italian Institute for Genomic Medicine

AZIENDA OSPEDALIERO-UNIVERSITARIA Città della Salute e della Scienza di Torino
S.C. Oncoematologia Pediatrica
Ospedale Infantile Regina Margherita

SAR-GEN_ITA - Studio multicentrico prospettico per l'analisi del profilo genomico di pazienti affetti da sarcomi alla diagnosi e/o alla ricaduta/ refrattarietà di malattia

- Sarcomi alla diagnosi o recidivati / refrattari
- *Torino*

PNRR 2023 – Genom-ACT

Ministero della Salute
Direzione generale della ricerca e dell'innovazione in sanità
PNRR: M6/C2_CALL 2023 Full Proposal

Finanziato dall'Unione europea
NextGenerationEU

Project Code: PNRR-TR1-2023-12377666	**Call section:** Tumori Rari
Applicant Institution: Piemonte	**Applicant/PI Coordinator:** Fagioli Franca

1 - General information

Project code: PNRR-TR1-2023-12377666

Project topic: C2) Tumori rari: sviluppo di soluzioni trasversali che possano avere impatto su molteplici patologie in termini di ricerca e assistenza

Applicant Institution: Piemonte

PI / Coordinator: Fagioli Franca

Istitution that perform as UO for UO1: Piemonte - Pediatric Onco-Hematology Department Regina Margherita Children's Hospital, AOU Città della Salute e della Scienza di Torino

Call section: Tumori Rari

Proposal title: A national multicenter pediatric framework and digital infrastructure to foster the genomic approach for children and adolescents with high-risk solid tumors.

Duration in months: 24

MDC primary: Oncologia

MDC secondary: Pediatria

Project Classification IRG: Genes, Genomes and Genetics

Project Classification SS: Molecular Genetics - MGA

1. **Ospedale Infantile Regina Margherita, Torino**
2. Fondazione IRCCS Istituto Tumori, Milano
3. AOU Policlinico G. Rodolico-San Marco, Catania
4. Ospedale Pediatrico Microcitemico, Cagliari

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AcSé ESMART (ITCC-057)

International, multi-center, open-label, prospective, phase I/II dose-validation study with a RP2D confirmation part, which is open to being expanded to refine an efficacy assessment for each agent

- **Coordinating Investigator:** Dr Birgit Geoerger
- **Co-sponsors:** Spain, Italy, United Kingdom, Netherlands, Germany, Denmark
- 15 - 20 phase 1 ITCC centers

- Recruitment period : 108 months (9 years)
- Follow-up period : 24 month after the last inclusion
- **Planned study duration :** 132 months (**11 years**)
- **Study population:** children, adolescents and young adults with refractory or recurrent malignancies
- **Number of patients**: **~ 450**

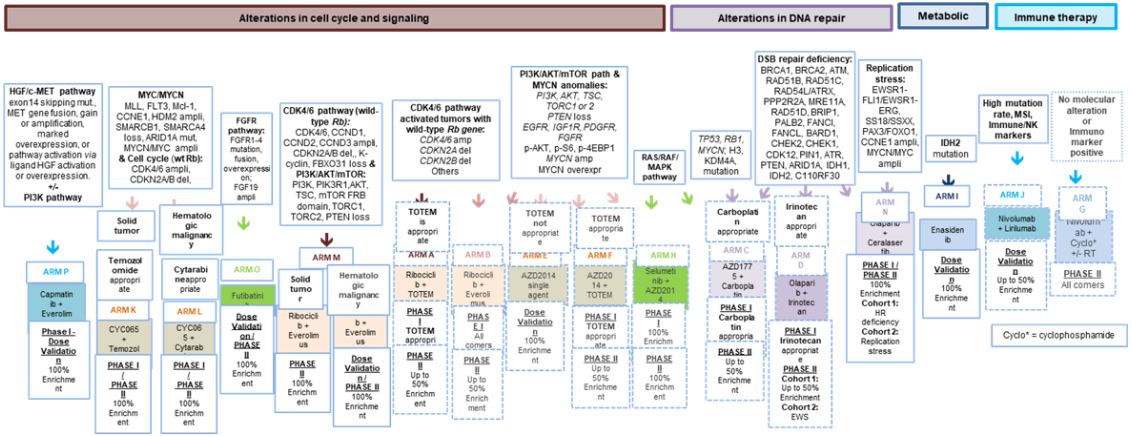
AcSé ESMART (ITCC-057)

Patients with relapsed or refractory hematologic or solid tumor malignancy with extensive molecular analysis

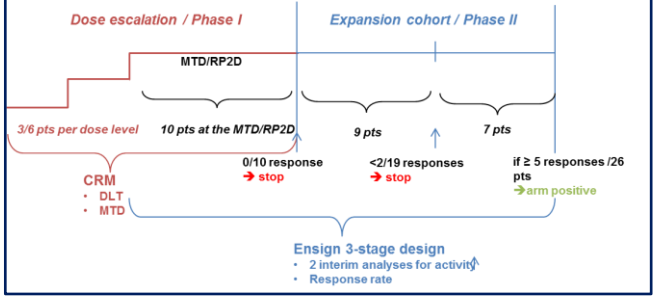
e-smart — European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children

Patients whose tumor present

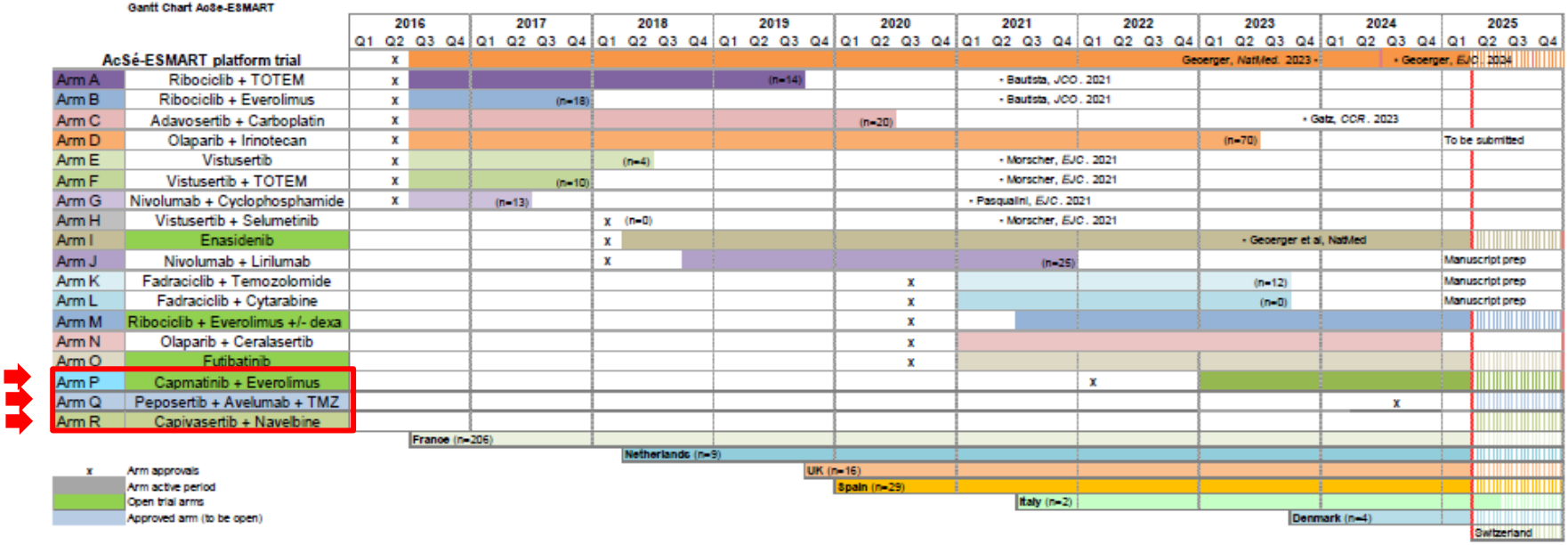
Key Inclusion criteria
- Age < 18 years at inclusion
- Evaluable/measurable disease
- Lansky/Karnofsky ≥70%
- Adequate organ function
- Absence of ≥ G2 toxicities
- Adequate "wash-out" of previous therapies



- Each arm is conducted independently
- Phase I part and phase II part
  - Assess **toxicity** (DLT, MTD, RP2D) and **activity**



AcSé ESMART (ITCC-057)

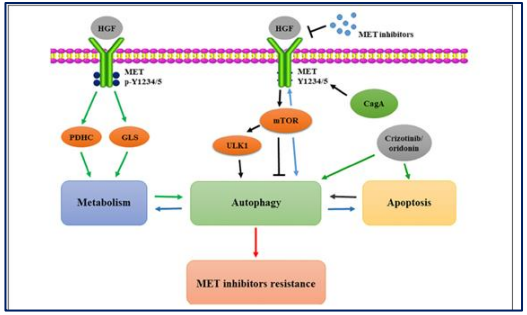


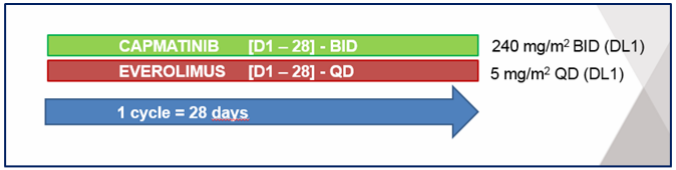
Protocol Version 8.0 – 8th July, 2025

- 18 arms since 2016
- 3 arms open to enrolment (P, Q, R)
- 8 arms with already published results

Arm P – Capmatinib (METi) + Everolimus

- Capmatinib (INC280) demonstrated significant activity in **c-MET activated tumor**, mainly with **MET exon 14 skipping mutations or MET gene fusion**
- Combined inhibition of c-MET with its downstream PI3K/mTOR pathway may reduce resistance and exhibit superior activity, particularly in high grade glioma
- First-in-child





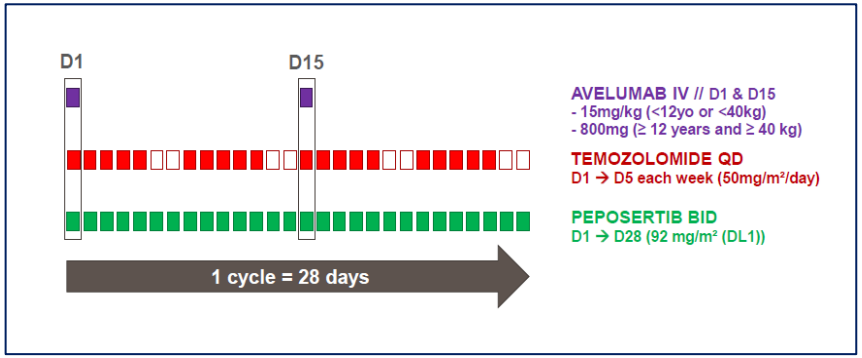
Molecular enrichment for potential biomarkers

- ***MET*** exon 14 skipping mutations, *MET* fusion, (focal or large), *MET* gain or amplification, marked MET overexpression, or MET pathway activation via overexpression or activation of the ligand HGF
- Tumors with co-occurrence of mutations in the **PI3K pathways** such as *PIK3CA, PIK3R1*, *AKT*, *TSC or mTOR FRB* domain (excluding kinase domain) mutations, gain of *AKT* or loss of *PTEN* are prioritized

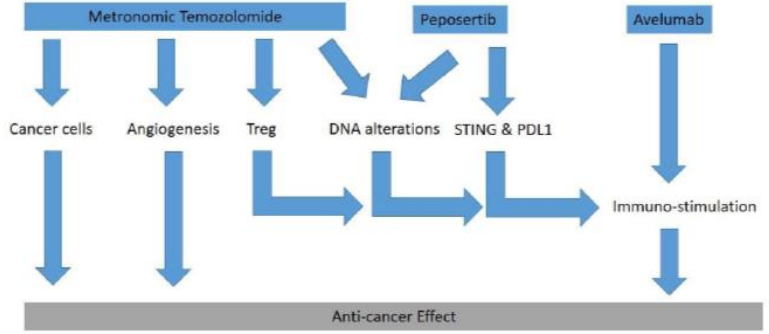
	Capmatinib orally BID Days 1-28 of a 28 day cycle	Everolimus orally QD Days 1-28 of a 28 day cycle
DL -2:	100% single agent adult equivalent RP2D	50% single agent pediatric RP2D
	Capmatinib: 240 mg/m² BID	**Everolimus:** 2.5 mg/m² QD
DL -1:	100% single agent adult equivalent RP2D	75% single agent pediatric RP2D
	Capmatinib: 240 mg/m² BID	**Everolimus:** 3.5 mg/m² QD
DL 1:	100% single agent adult equivalent RP2D	100% single agent pediatric RP2D
	Capmatinib: 240 mg/m² BID	**Everolimus:** 5 mg/m² QD

Arm Q – Avelumab + Peposertib + Temozolomide

- **Avelumab**
  anti-PD-L1 antibody, with clinical activity in various tumors
- **Peposertib**
  oral, small-molecule, selective DNA-PK inhibitor
  Deoxyribonucleic acid protein kinase (DNA-PK) plays a critical role in the repair of DNA double strand breaks (DSB)
- **Metronomic temozolomide**
  activity in many pediatric solid tumors
  potential to deplete T-reg in vivo.
  as an alkylating agent it induces DNA damage.
  It can perturb tumoral neoangiogenesis



It is hypothesized that the triplet could improve anti-PD1 activity through increase in the number of neoantigens at the tumor level and by depleting T-regs



Arm Q – Avelumab + Peposertib + Temozolomide

Molecular enrichment for potential biomarkers

For peposertib: **any activating alteration in the DNA repair pathways** including but not limited to:

- **any deleterious alteration in the HR pathway** that is related or putatively linked with deficiency including but not limited to BRCA1, BRCA2, ATM, RAD51B, RAD51C, RAD54L/ATRX, MRE11A, RAD51D, BRIP1, PALB2, FANCI, FANCL, BARD1, CHEK2, CHEK1, CDK12, PIN1, ATR, PTEN, ARID1A, IDH1 or IDH2, amplification of C110RF30 (EMSY gene; CAD22881), or **alterations consistent with strong replication/transcription stress** including but not limited to EWSR1::FLI1/EWSR1::ERG, SS18::SSXX, PAX3::FOXO1 gene fusions, CCNE1 amplification, MYCN or MYC amplification.
- **alteration in PI3K pathway** such as but limited to (PI3K, PIK3R1, PTEN, AKT, mTOR, PDK1, 4EBP1, eIF4)

For immunotherapy:

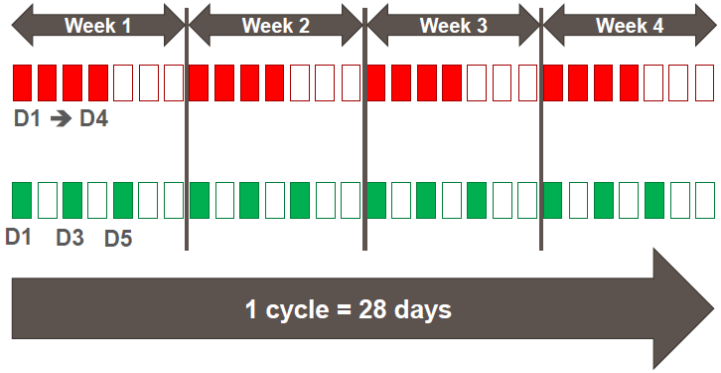
- **high mutation rate** i.e. high tumor mutational burden (>10 somatic mutations/Mb)
- **high MSI status** (alteration of MLH1, MSH2, MSH6 or PMS2)
- **immunomarker positive (PD-L1 ≥1%)** or previous PR, CR or SD for at least 6 month to anti-PD1/Anti-PDL1 inhibition treatment

Arm R – Capivasertib + Vinorelbine

- **Capivasertib** is an oral, potent, selective ATP-competitive **pan-AKT kinase inhibitor** that has shown promising activity in adult solid tumors and significant activity in vitro and in vivo in several pediatric tumor types
- **Metronomic vinorelbine** has a broad spectrum of activity in adult and pediatric cancer
- **Synergistic activity** observed when combining AKT inhibitors and microtubules targeting agents (taxanes & vinca-alkaloids)

Molecular enrichment for potential biomarkers

PI3K/AKT/mTOR pathway activation including but not limited to: PI3KCA, AKT mutations, amplification, gene fusions, PTEN deleterious mutation or loss. MYC/MYCN amplification or mutations, EGFR, IGF1R, PDGFR, FGFR, etc. mutations, amplifications or gene fusions, p-AKT, p-S6, p-4EBP1, PTEN loss (IHC) may also potentially be considered for pathway activation.



HEM – iSMART (ITCC-104)

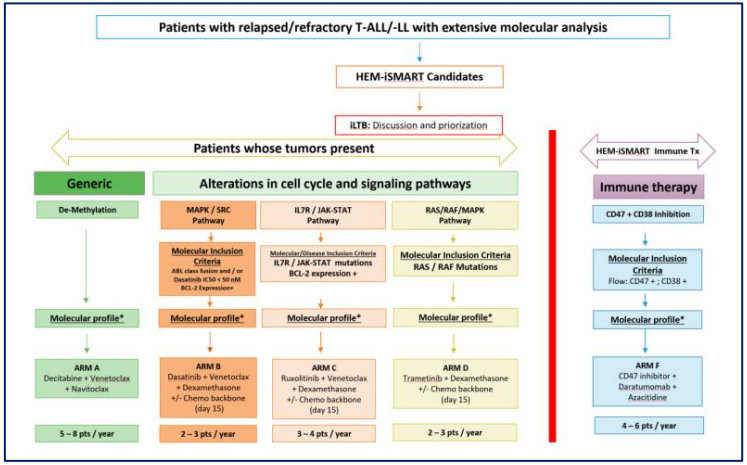
International proof of concept therapeutic Stratification trial of Molecular Anomalies in Relapsed or Refractory Hematological malignancies in children

Sponsor:
PRINCESS MAXIMA CENTER

Lead clinicians: Dr. Paco BAUTISTA, Dr. Andrej LISSAT, Prof. Michel ZWAAN

- Multi-arm, actionable target-driven phase I/II clinical trial for **relapsed/refractory acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL)**
- 36 sites across 14 European countries

- **Group B**: Dasatinib, Venetoclax, Dexamethasone (ABL-like)
- **Group C**: Ruxolitinib, Venetoclax, Dexamethasone (IL7R and JAK-STAT)
- **Group D**: Trametinib, Dexamethasone (MAPK pathway)
- **Group E**: Capivasertib, Venetoclax, Dexametasone (unselected pts, PI3K/AKT/mTOR)



INFORM 2 (ITCC-104)

INFORM 2 exploratory multinational, multi-arm phase I/II basket trial

KiTZ Hopp-Kindertumorzentrum Heidelberg

Sponsor:
HEIDELBERG UNIVERSITY HOSPITAL

Lead clinician: Dr. Cornelis VAN TILBURG

INFORM2 NivEnt
combination of nivolumab and entinostat in children and adolescents with refractory high-risk malignancies

- **Nivolumab**: immune-checkpoint inhibitor (anti PD-1)
- **Entinostat**: class I selective HDAC inhibitor

- age 2-21 years
- refractory/relapsed/progressive high-risk malignancies

- *Germany, Austria, Switzerland, Sweden, France, Australia*

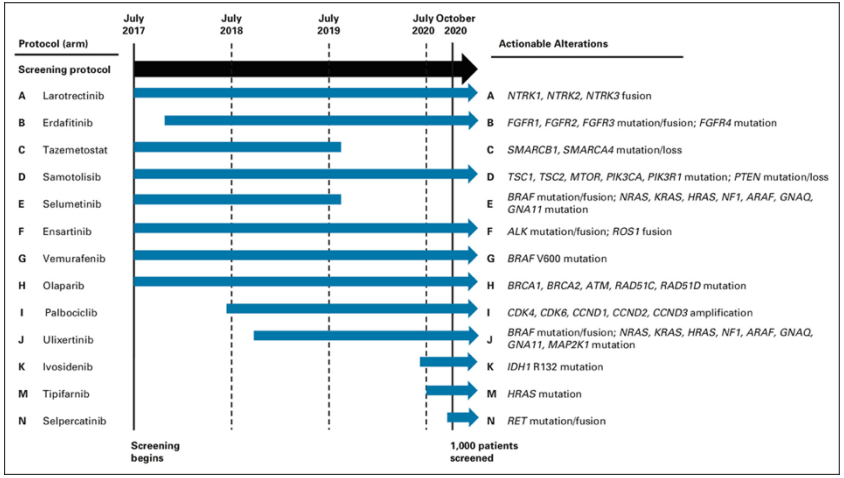
Group A:
a high mutational load (> 100 somatic SNVs/exome)

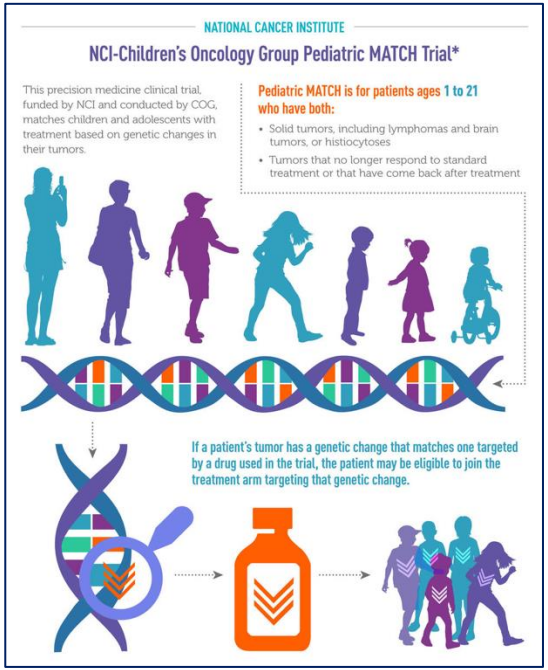
Group C:
focal MYC(N) amplification or ATRT-MYC subgroup

Group E:
high T-cell infiltration (> 600 cells/mm²)

NCI-COG Pediatric MATCH trial

- Precision medicine for children in USA
- Advanced solid tumors
- Age 1-21 years
- Started in 2017 and opened in 200 centers
- **>1300 patients enrolled**
- **13 treatment arms**
- Last arm: ensartinib (ALK, ROS1)





Joint Action Personalised Cancer Medicine

Overview

Funding EU4Health: €±25 million

Total: €31.6 million

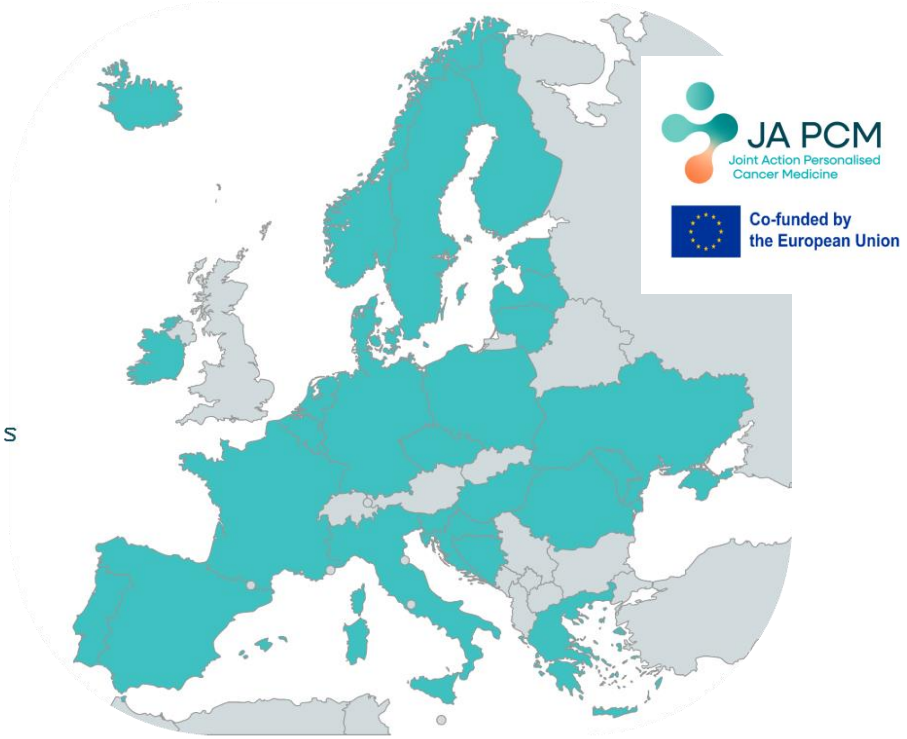
Duration Nov 2025 - Oct 2029

Project Lead Sciensano, Belgium

Consortium 145 Partners and 29 countries

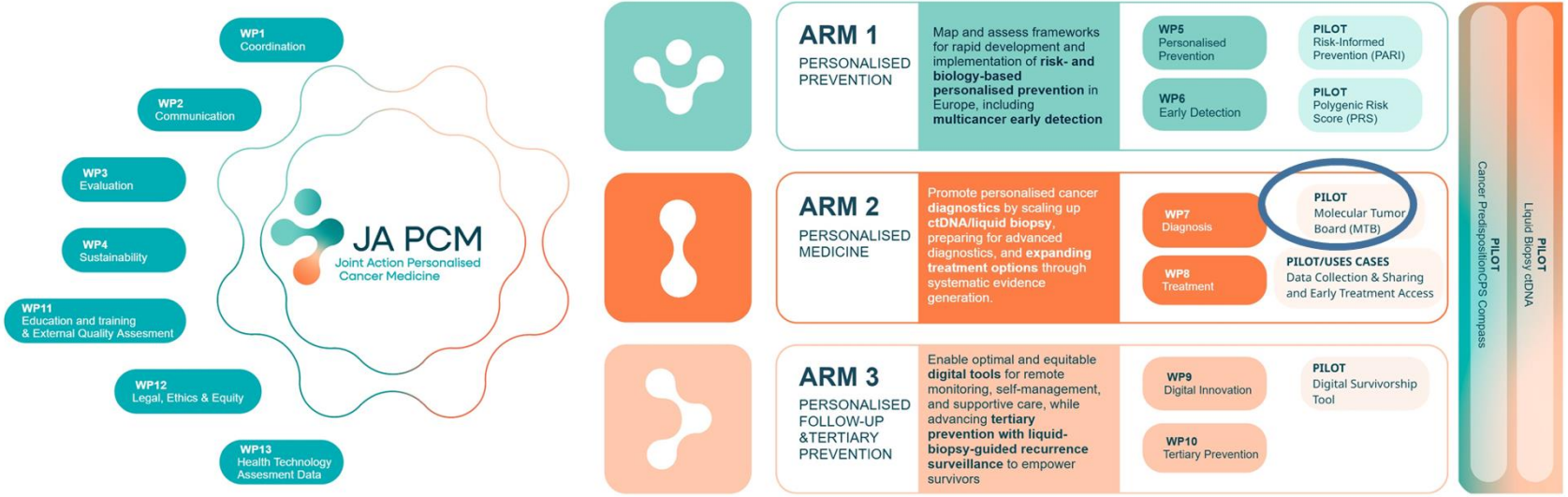
- 71 Medical Care Organisations
- 41 Research Organisations
- 32 Public & Governmental Organisations
- 5 Professional Networks
- 2 Patient Organisations

Builds on can.heal, PCM4EU Personalised Cancer Medicine for all EU Citizens



Joint Action Personalised Cancer Medicine

Action Plan



Pilot #3: Supranational molecular tumor board for complex cases/countries without MTB

ITALIA – Molecular Tumor Board regionali

Il **30 maggio 2023** è stato approvato il **Decreto** del Ministero della Salute *«Istituzione dei Molecular Tumor Board e individuazione dei centri specialistici per l'esecuzione dei test per la profilazione genomica estesa Next Generation Sequencing (NGS)»*.

Il percorso di istituzione del Molecular Tumor Board Regionale è stato avviato partendo dal contesto regionale caratterizzato da elevata complessità, elevate competenze e disponibilità di tecnologie di ultima generazione.

23A04613

MINISTERO DELLA SALUTE

DECRETO 30 maggio 2023.

Istituzione dei *Molecular tumor board* e individuazione dei centri specialistici per l'esecuzione dei test per la profilazione genomica estesa *Next generation sequencing* (NGS).

IL MINISTRO DELLA SALUTE

Vista la legge 23 dicembre 1978, n. 833, di istituzione del Servizio sanitario nazionale;

Visto l'art. 12, comma 2, del decreto legislativo 30 dicembre 1992, n. 502, che stabilisce che una quota pari all'1% del Fondo sanitario nazionale è destinata al finanziamento di iniziative previste da leggi nazionali o dal Piano sanitario nazionale riguardanti programmi speciali di interesse e rilievo interregionale o nazionale per ricerche o sperimentazioni;

Visto l'art. 4 del decreto legislativo 30 giugno 1993, n. 266, «Riordinamento del Ministero della sanità, a norma dell'art. 1, comma 1, lettera *h)*, della legge 23 ottobre 1992, n. 421»;

European development strategy

1. Generate invididual molecular information at relapse

Molecular Matching Trials

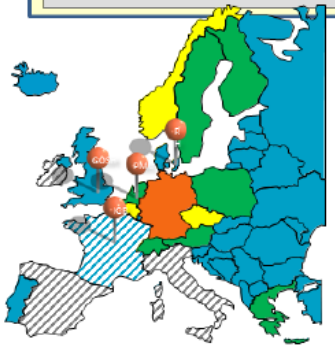
- MAPPYACTS > FMG2025 MAPPYACTS 2 (France, Spain, Italy, Ireland > + Denmark, Lithuania)
- INFORM (Germany, Austria, Sweden, Switzerland, Belgium)
- iTHER (The Netherlands)
- SM-PAEDs (UK)

MATCH

Match treatment and tumor profile

3. Evaluate activity of drugs and combinations

- Phase 1 Trials (Industry and ISTs)
- Phase 2 Trials (Industry and ISTs)
- Genentech Roche Matrix Trial
- AcSé-ESMART Multiarm trial
  European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children (ESMART)
- INFORM2 trial series



SHARE

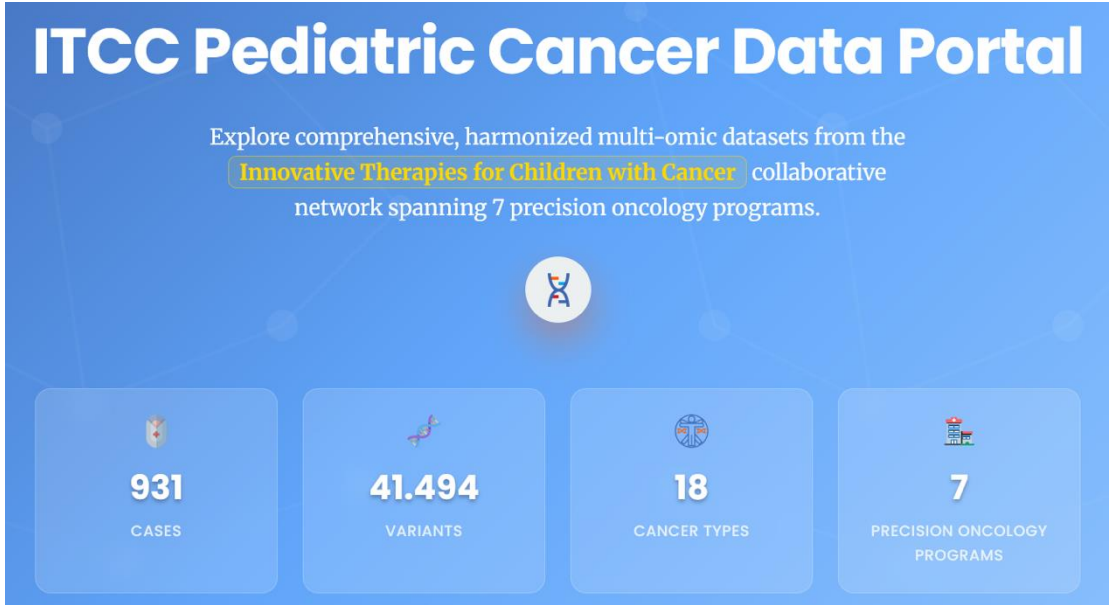
EU Clinico Biological
(WES/RNAseq
Data Base

Project A
Project B
Project C
Project D

Pediatric New Drug Development

4. Generate new knowledge, new druggable pathways

European development strategy



Coordinated by Princess Máxima Center pediatric oncology — dkfz. German Cancer Consortium Core center Heidelberg

Funded by Dietmar Hopp Stiftung

ITCC pediatric cancer data portal

- Started in **2015** by **7 national pediatric precision oncology programs** running in Europe, Canada and Australia
- **Objective:** To provide federated access to complete sequencing of pediatric malignancies (WGS, WES, RNAseq, Methylome)

European development strategy

ITCC Pediatric Preclinical Proof-of-concept Platform (**ITCC-P4**)

Potenziali limiti della medicina di precisione

- Alti costi delle analisi
- Tempo lungo per l'ottenimento dei risultati
- Potenziali complicanze di prelievi tissutali evitabili
- Limitata disponibilità di farmaci e accessibilità a trials clinici
- Eccessive aspettative da parte dei pazienti
- Dubbio beneficio prognostico

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Limits to Personalized Cancer Medicine

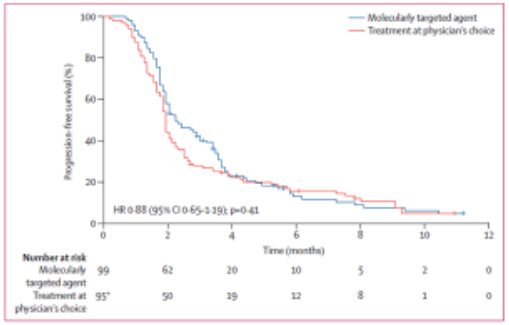
Ian F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.

N Engl J Med 2016; 375:1289-1294 | September 29, 2016 | DOI: 10.1056/NEJMsb1607705

SHIVA trial

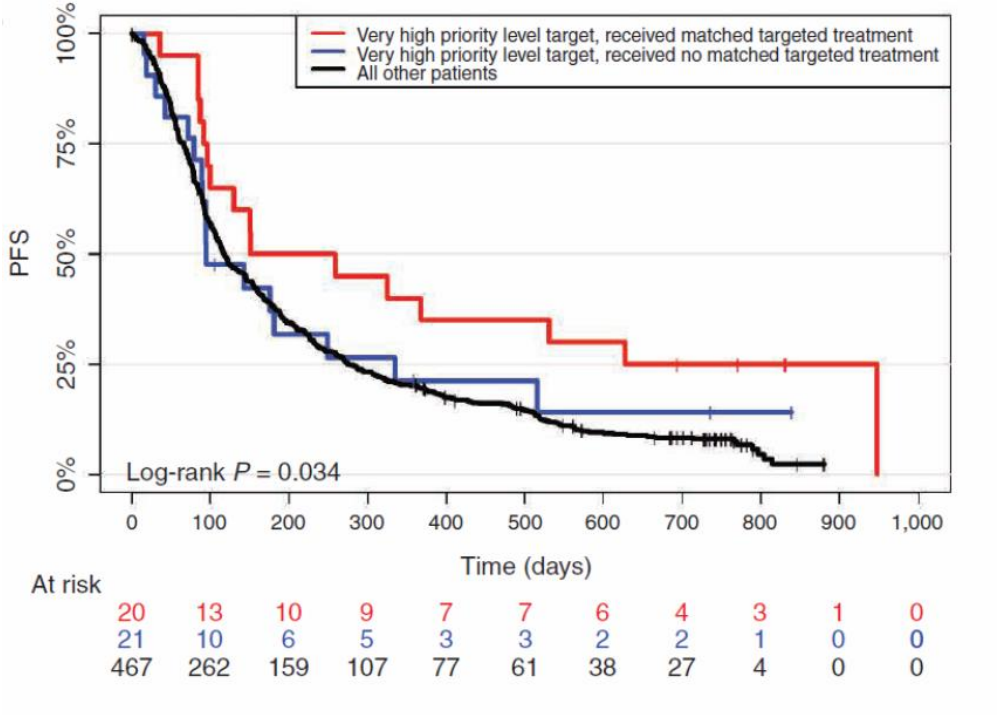
Randomized trial of matched molecular targeted treatment or physician's choice

No significant difference in PFS, HR for death or disease progression



Le Tourneau C et al. Lancet Oncol. 2015

INFORM registry



The **highest target priority level** was observed in 42 of 519 patients (**8.1%**)
Of these, 20 patients received matched targeted treatment with a **median PFS of 204 days, compared with 117 days in all other patients**

Van Tilburg CM et al. Cancer Discov 2021

Real world data

Original Reports | Precision Medicine

Real-World Outcomes of Molecular Tumor Board Treatment Recommendations

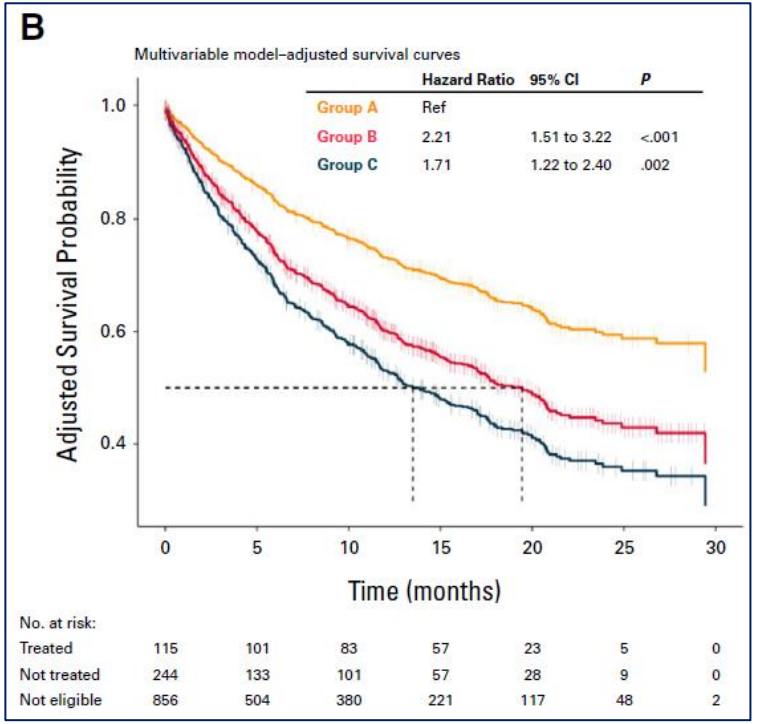
Federico Nichetti, MD[1,2]; Marta Brambilla, MD[1]; Matteo Duca, MD[1]; Alberta Piccolo, PhD[3]; Daniela Miliziano, MD[1]; Chiara Cavalli, MD[1]; Francesca Marra, MD[3]; Paolo Ambrosini, MD[1]; Caterina Zanella, MD[1]; Claudio Vernieri, MD, PhD[1,4]; Daniele Lorenzini, MD[3]; Elena Colombo, MD[1]; Silvia Damian, MD[1]; Paolo Baili, BSc[5]; Claudia Proto, MD[1]; Adele Busico, PhD[3]; Elena Conca, BSc[3]; Iolanda Capone, BSc[3]; Siranoush Manoukian, MD[6]; Elena Tamborini, BSc[7]; Federica Perrone, MD[7]; Monica Niger, MD[1]; Andrea Vingiani, MD[3,8]; Luca Agnelli, MD[1,3]; Filippo de Braud, MD[1,8]; and Giancarlo Pruneri, MD[3,8]

- Clinical relevance of molecularly targeted agents treatment (MTAs) in patients discussed by the MTB of the National Cancer Institute of Milan
- 2021-2022: **1813 cases** in 18 months
- Patients were stratified into:

  eligible to MTA and treated (group A)

  eligible to MTA but not treated (group B)

  not eligible (group C)



- ***Median PFS*** on MTA: 12.0 months
- ***Median PFSratio*** in patients receiving MTA: 2.71, with a **benefit rate of 64%**
- **OS was significantly longer in group A** than in B and C patients

Nichetti F et al. JCO Precis Oncol 2025

Patient's expectations

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer SIOP aspho

Patient/parent perspectives on genomic tumor profiling of pediatric solid tumors: The Individualized Cancer Therapy (iCat) experience

- 89% hoped participation would help find cures for future patients
- 59% hoped participation would increase their/their child's chance of cure

- Participants in pediatric molecular profiling studies perceive benefits for themselves and others, but ***expectations of personal benefit exceed actual positive impact***

Necessity to improve communication during consent discussion to increase patient's awareness about molecular research participation

Marron J et al. PBC 2016

Conclusioni

- Progressi nell'analisi avanzata di profili molecolari tumorali pediatrici e nella somministrazione di trattamenti sulla base di essi

- Possibilità di incrementare il numero di pazienti arruolati nei trials clinici e facilitare l'accesso all'utilizzo di farmaci innovativi

- Incremento delle conoscenze sulla genetica e la biologia delle neoplasie pediatriche e potenziale definizione di nuove strategie e target terapeutici specifici

- Impegno e attenzione per fare sempre prevalere l'interesse del paziente rispetto a quello della ricerca e del ricercatore (selezione e comunicazione)

Settima edizione di

G.d.L. Biologia Cellulare Molecolare

AIEOP

ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP...

...in Lab

Milano, 22 e 23 maggio 2026